Published in final edited form as:

Toxicology. 2017 May 15; 383: 24–39. doi:10.1016/j.tox.2017.03.020.

Immune-related Gene Polymorphisms in Pulmonary Diseases

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Abstract

Between the DNA sequences of two randomly-selected human genomes, which consist of over 3 billion base pairs and twenty five thousand genes, there exists only 0.1% variation and 99.9% sequence identity. During the last couple of decades, extensive genome-wide studies have investigated the association between single-nucleotide polymorphisms (SNPs), the most common DNA variations, and susceptibility to various diseases. Because the immune system's primary function is to defend against myriad infectious agents and diseases, the large number of people who escape serious infectious diseases underscores the tremendous success of this system at this task. In fact, out of the third of the global human population infected with *Mycobacterium tuberculosis* during their lifetime, only a few people develop active disease, and a heavy chain smoker may inexplicably escape all symptoms of chronic obstructive pulmonary disease (COPD), lung cancer, and other smoke-associated lung diseases. This may be attributable to the genetic makeup of the individual(s), including their SNPs, which provide some resistance to the disease. Pattern recognition receptors (PRRs), transcription factors, cytokines and chemokines all play critical roles in orchestrating immune responses and their expression/activation is directly linked to human disease tolerance. Moreover, genetic variations present in the immune-response genes of various ethnicities may explain the huge differences in individual outcomes to various diseases and following exposure to infectious agents. The current review focuses on recent advances in our understanding of pulmonary diseases and the relationship of genetic variations in immune response genes to these conditions.

Keywords

TLRs; NLRs; Transcription Factors; Cytokines; Chemokines

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Conflict of Interest: The authors declare no conflict of interest.

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Introduction

The complexity of the immune system, the intrinsic genetics, polymorphisms and interactions with the extrinsic environment, are all predetermined factors governing disease progression and pathogenic outcome. The generation of a balanced immune response by the host is critical to counter environmental factors, and genetic variations can result in varied outcomes.

Before the widespread use of rapid sequencing techniques, the primary focus of research was to determine the presence or absence of specific genes or to observe their level of expression (transcription and translation) in response to stimuli. Due to this approach, genetic diseases were considered rare compared to physiological causes of disease. However, with the innovations in sequencing protocols and technological advancements, detailed understanding of the genetic variability between individuals, and even between cells, and the connection of these variations to disease outcomes has been revealed. It is now becoming apparent that genetic polymorphisms are not only an important factor in disease development, but also can be employed as biomarkers. Clinically, biomarkers are used as prognostic indicators as well as precautionary markers for some diseases (McGeough and Bjorson, 2013).

Various studies discussed in this review have demonstrated significant association of SNPs present in immune genes with increased susceptibility to diseases and infections. Additionally specific SNPs can be associated with the survival rate of the patient after treatment. Therefore, understanding genetic variations in key players of the immune system can have far-reaching effects on pathophysiology. The most frequently found variations in the genome include single-nucleotide polymorphism (SNPs), which arise from mutations and provide another level of diversity (Brookes, 1999).

Several SNPs in the genome are known to be responsible for complex phenotypes in terms of medical relevance, and may significantly affect multiple molecular pathways important in the adaptation of related individuals (Figure 1) (Viana et al., 2015). Polymorphisms present in the DNA sequences of intergenic spacers are not lethal to organisms and are considered both stable and heritable. However, polymorphisms that cause changes in the amino acid sequence are called non-synonymous changes and may lead to alterations in protein structures and function (Cargill et al., 1999; Sunyaev et al., 2000). Of these, the SNPs that are linked to phenotypic risks and are within genes of functional importance are considered for association studies (Yuan et al., 2006). SNPs may influence protein conformation, promoter activity or pre-mRNA and RNA splicing.(Cartegni and Krainer, 2002; Prokunina et al., 2002).

Those SNPs present at transcription factor binding sites in the promoter or intronic enhancer regions can also influence transcriptional regulation (Prokunina and Alarcón-Riquelme, 2004; Prokunina et al., 2002). Moreover, SNPs may also function by disrupting exonic splicing enhancers or silencers (Cartegni and Krainer, 2002). Therefore, each individual SNP in a gene might exert a different effect on pathophysiology. SNPs have been identified in several genes (~582 genes) known to play crucial roles in human survival by interfering with

metabolism and immunological functions. Several of these are also known to regulate variable morphological characteristics in humans (Norrgard and Schultz, 2008). Furthermore, genetic variants can not only cause disease conditions, but also may provide resistance to infection and disease.

Interestingly, the genetic variability of pathogens allows them to switch host species leading to the spread of new strains, which is both a major veterinary and public health concern. The genetic alterations resulting in these adaptations are still being investigated (Viana et al., 2015), although in general it is believed that mutations help pathogens overcome various host challenges resulting in their rapid spread. During the recent Ebola outbreak in 2014 several SNPs, including amino acid changes, were identified and found to be unique to the new strains (Gire et al., 2014). Similarly, the ongoing Zika virus epidemic may be attributed to SNPs, which may adapt their codon usage bias to mimic that in humans (de Melo Freire et al., 2015). The focus of this review is to provide information about the genetic associations of immune-related genes with known significance in pulmonary diseases. Due to the occurrence of both protective and predisposing alleles for the same molecule, a comprehensive understanding of the molecular mechanisms associated with alterations in immune-related genes will be helpful for designing better therapeutic strategies to combat pulmonary diseases. To this end, we will discuss the role of SNPs associated specifically with pattern recognition receptors, transcription factors, cytokines, and chemokines.

1. Pattern Recognition Receptors (PRRs) and their impact on lung disease susceptibility

The Immune system consists of innate and adaptive arms that must act cooperatively to successfully combat a wide-variety of potentially detrimental external and internal stimuli and for healing of damaged tissue. The innate immune system contains PRRs that identify both pathogen-associated molecular patterns (PAMPs) and endogenous molecules released by damaged cells, termed damaged associated molecular patterns (DAMPs), to invoke inflammatory responses. The families of PRRs include transmembrane toll-like receptors (TLRs), C-type lectin receptors (CLRs), cytoplasmic nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), RIG-like receptor (RLR), membrane binding lectins, and the mannose receptor. Sensing of PAMPs or DAMPs by PRRs leads to downstream signaling events resulting in the activation of transcription factors and the production of proinflammatory cytokines and chemokines. During classical inflammation these events lead to increases in the permeability of the vascular endothelium and extravasation of immune cells followed by the termination of inflammatory responses and repair of damaged tissues (Kumagai and Akira, 2010). Orchestration of the inflammatory/immune response can be significantly altered by changes in the expression/activation of any of these components of the immune system. In this section we will systematically focus on recent advances in association studies linking SNPs in PRR genes with pulmonary diseases.

TLR genes family—TLRs are a class of proteins expressed on the membranes of immune and non-immune cells that recognize structurally-conserved molecules within microbes. Recognition of PAMPs by TLRs leads to the initiation of signaling pathways resulting in the activation of the innate immune response and the development of acquired immunity.

Variations in TLRs may influence their expression levels and their function leading to an increase in disease susceptibility.

The association of genetic variations in TLRs with *Mycobacterium tuberculosis* infection (TB disease) has been studied in Asians, African-Americans, Caucasians, and other populations (Najmi et al., 2010; Velez et al., 2010). Moreover, allele A of rs352139 (+1174 A/G) located in the intronic region of *TLR9* was found to be significantly associated with tuberculosis. In Mexican Amerindians, the dominant A/A and A/G genotypes are coupled with an increased risk of disease, particularly in females; while the frequency of the G/G genotype was found to be very low in tuberculosis patients indicating a potentially protective role of this allele (Torres-García et al., 2013). Likewise, SNP allele A of rs352139 in the A allele also showed a strong link with TB susceptibility in Indonesian females (Kobayashi et al., 2012). Other reports have suggested that polymorphisms in *TLR2* and *TLR9* influence susceptibility to pulmonary tuberculosis in Caucasians and Africans, and in African-Americans, respectively (Velez et al., 2010). Further, the frequency of a homozygous C/C genotype at position rs3804100 (+1350 T/C) of the *TLR2* gene was significantly high in patients with latent tuberculosis infections (LTBI) whereas the G/A genotype of SNP rs5743708 (2258 G/A) was coupled with pulmonary tuberculosis. Moreover, occurrence of the C/C genotype at position rs3764879 (−129 C/G) in *TLR8* and G/G genotype at rs7873784 (+12186 C/G) in *TLR4* was significantly higher in TB patients in a Chinese population (Wu et al., 2015). In another report, the G allele of SNP rs5743618 (1805 G/T) in the *TLR1* gene was related with an increased risk of tuberculosis in Han Chinese from North China (Qi et al., 2015) (Table 1).

Genetic variations in TLRs have also been associated with chronic obstructive pulmonary disease (COPD). COPD refers to two lung conditions: chronic bronchitis and emphysema. These conditions are characterized by progressive obstruction of airflow which interferes with normal breathing and is associated with an abnormal lung inflammatory response due to stimulants including cigarette smoke (CS) (Kahraman et al., 2013). In COPD, disease acute exacerbations (AEs) are the major cause of morbidity and mortality. The −1486 T/C and −1237 T/C genetic variants in the promoter region of the *TLR9* gene have been investigated for their association with COPD. In a German population, the frequency of the C allele at position −1486 T/C was significantly high in COPD patients whereas SNP −1237 T/C was not found to be associated with COPD (Pabst et al., 2013). In addition, a rs4986791 (+1196C/T or Thr399Ile) variation in the *TLR4* gene was linked with a 2.4-fold increase in the risk of COPD development in Greek smokers (Speletas et al., 2010) (Table 2).

Asthma is characterized by excessive inflammation and increased production of sticky secretions inside bronchial tubes leading to reversible airflow obstruction and bronchospasm. Genetic variations in the *TLR4* gene were assessed for their association with asthma, and individuals carrying a T allele at SNP rs4986791 (+1196C/T or Thr399Ile) were found to be resistant to asthma in a North Indian population whereas no association was found between the rs4986790 (+896A/G or Asp299Gly) polymorphism and asthma in the same population (Sinha et al., 2014). Another report demonstrated that patients with the T/T homozygous genotype of rs7656411 (22215T/G) in the *TLR2* gene exhibited a significantly lower risk of asthma compared to those that were G/G homozygous at this position.

Moreover, for allergic rhinitis, a disease condition that frequently coexists with asthma, allele T at position rs2381289 (4224C/T) in *TLR6* was positively associated, whereas allele A at position rs11466651 (Val298Ile, c.892G/A) in *TLR10* was negatively associated with disease (Qian et al., 2010) (Table 3).

NLR family genes—NLRs play a crucial role in the initiation of inflammatory responses following recognition of PAMPs or DAMPs (Martinon et al., 2009). In humans more than 22 NLRs have been identified and SNPs within their genes have been found to be associated with several diseases (Fritz et al., 2006; Zhao et al., 2012). The N-terminal caspase recruitment domain (CARD) and pyrin domain (PYD) of NLRs play important roles in the regulation of downstream signaling cascades leading to the activation of transcription factors and production of pro-inflammatory mediators (Becker and O'Neill, 2007). Polymorphisms in NLRs have received a great amount of attention in recent years. For example, a polymorphism in the *NOD2* gene has been shown to play an important role in susceptibility to *Mycobacterium tuberculosis*. However, an association between an exon 4 polymorphism and TB infection have been studied in different population but its association was not found consistent in all populations (Austin et al., 2008; Khalilullah et al., 2014). Three common non-synonymous SNPs of the *NOD2* gene, which replace amino acids Pro268Ser (rs2066842), Arg702Trp (rs2066844) and Ala725Gly (rs5743278), are associated with TB in the African American population. Amongst these, Pro268Ser and Arg702Trp provide resistance to the host against TB infection, whereas Ala725Gly increases susceptibility to the disease (Austin et al., 2008) (Table 1). Moreover, the Arg702Trp and Gly908Arg SNPs were not found associated with TB infection in the South African population (Möller et al., 2007).

Genetic polymorphisms in *NOD1* and *NOD2* (*CARD15*) genes were also found to be associated with the pathophysiology of COPD and allergic asthma. Amongst these, the intron variant of *NOD2*, allele (rs1077861) A/T, was found to be associated with the development and progression of COPD in a Japanese population (Kinose et al., 2012) (Table 2). Three functionally relevant SNPs in *NOD2*, including rs2066844 (Arg702Trp), rs2066845 (Gly908Arg) and rs869147565 (Leu1007Pro), have been studied in school children in Germany. These SNPs are believed to hinder the pattern recognition of LPS and may be responsible for the development of asthma and allergies in children. It was also reported that children carrying the +2722C allele show a three-fold increase in susceptibility to allergic rhinitis, while those carrying the 2104T genotype allele in *NOD2* show a two-fold increase. Moreover, the risk of atopy is increased 50% in children carrying a C allele at the 3020insC frame shift in *NOD2* (Kabesch et al., 2003) (Table 3). Another study performed in a Caucasian adult population showed that the T allele of SNP rs1077861 in *NOD2* was coupled with a decreased risk of asthma development whereas the A genotype of rs3135500 in the same gene was significantly associated with increased risk of disease. Further, in the same study the A allele of rs5743266 or T allele of SNP rs2066842 (802C/T) in *NOD2* were found to be associated with a significantly-reduced risk of development of allergic rhino conjunctivitis (Weidinger et al., 2005). In addition, intron variant rs4612666 of *NLRP3* is significantly associated with Aspirin-intolerant asthma (AIA) (Hitomi et al., 2009).

Mannose-binding lectin (MBL)—MBL plays a crucial role in opsonin-induced phagocytosis and activation of the lectin pathway of the complement system (Gong et al., 2007). Two SNPs in MBL, rs69287125 and rs137824326, were studied for association with pulmonary tuberculosis in a Chinese population. The observations from this study revealed that allele G for both SNPs was protective, whereas allele A was a risk factor for pulmonary tuberculosis. It was also reported that the homozygous haplotypes of A/A and G/G in SNPs rs69287125 and rs137824326 were associated with pulmonary tuberculosis susceptibility (Bing et al., 2012) (Table 1).

The A/B genetic polymorphism in *MBL2* codon 54 was assessed for an association with asthma in North Indian populations. In this regard, the wild type A allele was found to be significantly associated with asthma (Birbian et al., 2012). In another study, SNPs in the *MBL* gene including 816 A/G, 868 C/T, 875 G/A, 884 G/A and 1011 G/A and *Surfactant Protein-D (SP-D)*-341 T/C were studied in an Indian population. Of these the G allele of SNPs 1011 G/A in *MBL* and the C allele at 341 T/C in the *SP-D* gene were found to be significantly associated with atopic asthma, while the genotype 1011 G/A polymorphism of *MBL* was associated with allergic rhinitis, asthma and Allergic Bronchopulmonary Aspergillosis (ABPA) (Kaur et al., 2006; Suman Latha et al., 2006). Patients homozygous for the 1011A allele showed significant increases in plasma MBL levels compared to those carrying the 1011G allele. Therefore, it was concluded that elevated levels of MBL may be associated with increased severity of bronchial asthma along with allergic rhinitis and ABPA (Kaur et al., 2006) (Table 3).

Mannose receptor—The mannose receptor (MR) plays a critical role in molecular-pattern recognition of polysaccharide structures of pathogens resulting in activation of the downstream, host immune response. MR is excessively expressed on alveolar macrophages and consists of one cysteine-rich domain and eight linked carbohydrate recognition domains (Gordon, 2003). SNPs in the mannose receptor C-type 1 (*MRC1*) gene have been shown to associate with varying expression and function of the protein thereby affecting an individual's susceptibility to pulmonary tuberculosis. SNPs in exon 7 of *MRC1*, rs34039386 (1186G/A) 1195G/A, 1212T/C, 1221C/G, 1303C/T and C1323C/T, were studied in a Chinese population in relation to tuberculosis susceptibility. It was observed that the frequency of the rs34039386 (1186G/A) allele was higher in the susceptible group than in the healthy controls showing a possible association with tuberculosis infection (Zhang et al., 2012a) (Table 1).

2. The role of transcription factors in pulmonary diseases

Inflammatory/immune responses involve multi-component coordinated mechanisms that determine the outcome of disease/infection. Selective translational control of effector molecules is a key regulatory step important for immunological function. Here, we provide an overview of the associations between variants of the widely-studied transcription factors nuclear factor- κ B (NF- κ B), p53, signal transducer and activator of transcription (STAT), retinoic acid receptor-related orphan receptor- α (ROR α), and fork head family of transcription factors (FOXO), all of which play critical roles in regulating immune/inflammatory responses during pulmonary diseases.

Nuclear factor- κ B (NF- κ B)—NF- κ B family of transcription factors regulate the expression of a wide variety of genes involved in a broad range of biological processes including inflammation, immunity, cell proliferation, differentiation, and survival (de Martin et al., 1999). Dysregulation of NF- κ B signaling can lead to inflammatory and autoimmune diseases as well as cancer. Therefore, SNPs in NF- κ B family members may crucially affect disease pathology (Sun and Zhang, 2007). Activation of NF- κ B is regulated by I κ B (inhibitor of kappa B), which regulates nuclear translocation and DNA binding of NF- κ B. The role of NF- κ B in modulating pathogenic outcomes of pulmonary diseases has also been well documented (Christman et al., 2000; Donovan et al., 1999; Sun and Zhang, 2007; Wright and Christman, 2003) SNPs identified in NF- κ B/I κ B consistently correlate with risk of COPD and lung cancer. Four putative functional SNPs in NF- κ B/I κ B (NF κ B1:-94 Insertion/Deletion ATTG Polymorphism; NF κ B2: -2966G/A; I κ B α : -826C/T, 2758G/A) were studied in southern Chinese populations. It was observed that individuals with the -94dins ATTG variant of NF- κ B 1 are more susceptible to development of COPD. The I κ B (2758G/A) SNP is associated with down regulation of I κ B α expression by modulating hsa-miR-449a (The microRNA-449 family is a group of three small, non-coding RNAs) and is linked with increased risk of lung cancer in certain Chinese populations (Huang et al., 2013) (Table 4). These studies show that assessment of genetic variations in NF- κ B and I κ B can be used to determine the susceptibility of certain populations to pulmonary diseases.

Transcription factor p53—The p53 transcription factor plays a vital role in cell cycle regulation, DNA repair, and apoptosis. The p53 response element (p53RE) has been shown to control p53 activation and plays an important role in susceptibility to cancer. Therefore, the effect of polymorphisms in the p53RE on p53-DNA binding was evaluated. One of the most studied polymorphism, rs1042522 (Arg72Pro, G/C), in the p53 gene is at codon 72 of exon 4, which codes for either arginine or proline (codon CGC/CCC). A correlation study of a Korean population showed that individuals carrying Arg/Pro and Pro/Pro were more susceptible to lung cancer as compared to those with the Arg/Arg genotype (Piao et al., 2011) (Table 4). However, another study revealed a significant association between polymorphisms in p53 and p21 (cyclin-dependent kinase inhibitor-1) and the occurrence of COPD. Moreover, the frequency of p53 Pro/Pro or Pro/Arg genotypes in comparison to the Arg/Arg genotype and p21 (rs1801270) also known as p21 codon 31 Arg/Arg or Arg/Ser genotypes compared to the Ser/Ser genotype were found to be significantly higher in COPD patients as compared to the smoker control group in Taiwanese patients (Lee et al., 2006) (Table 2).

Signal transducer and activator of transcription (STAT)—The signal transducer and activator of transcription (STAT) factors are a family of proteins involved in intracellular transcription that mediate several aspects of cellular immunity, apoptosis, differentiation, and cell proliferation. STAT3 variants, rs3816769 (+42240T/C or c.273+314A/G) and rs744166 (31313A/G or c.-1-13666T/C), have been found to be connected with lung cancer. Further, the CC genotype of rs3816769 and AA genotype of rs744166 are associated with decreased incidence of lung cancer, while the TT genotype of rs3816769 and GG genotype of rs744166 have been shown to be associated with a significantly elevated risk of lung cancer. Moreover, in non-small cell lung cancer (NSCLC) patients the A allele is rare,

showing a possible protective association of this allele, while the G allele is more frequent demonstrating a possible association of this allele with increased incidence of lung cancer (Domanska et al., 2013). In another study, SNPs rs4796793 (-1697C/G or c.-1915C/G in 5'UTR), rs7211777 (c.-2+6222C/T, intron variant), rs12949918 (c.-2+14024A/G, intron variant), rs744166 (31313A/G or c.-1-13666T/C), rs9912773 (c.-1-9999G/C, intron variant), rs3869550 (c.373-1460A/G, intron variant), rs2293152 (c.1233+43C/G, intron variant), and rs1053004 (c.*1671C/T, 3'UTR variant) in the STAT3 gene from the 5'-flanking region to 3'UTR were examined and it was reported that minor alleles (rs4796793 (-1697C/G), rs7211777, rs12949918, rs744166, rs9912773 and rs3869550) were associated with decreased risk of NSCLC as compared to homozygous carriers of common alleles. SNPs rs2293152 (intron 11, C/G) and rs1053004 (3' untranslated region, T/C) did not show any significant association with NSCLC (Jiang et al., 2011) (Table 4). Association of STAT3 mutations was studied in asthmatic children as well; however, overall the observations revealed that an effect of STAT3 mutations on serum IgE was unlikely (Wjst et al., 2009).

STAT1 exerts an anti-allergic function and SNP rs3771300 (c.2239-153A/C) of STAT1 was found to be inversely related to total serum IgE levels in German children. This was thought to protect these children from atopic sensitization (Pinto et al., 2007). The SNP rs2066807 (c.1782G/C, or Met594Ile) in STAT2, was found to be linked with asthma in Chinese and Taiwanese children (Hsieh et al., 2009) whereas three STAT3 SNPs, c.128+142G/T (rs2306581), c.-1-19390G/C (rs957971), and c.-2+10462T/C (rs1026916), were found to be strongly associated with reduced lung function in both asthmatic adults and children (Litonjua et al., 2005). However in another study, twenty-five STAT3 SNPs were analyzed for their association with high levels of total or specific serum IgE, elevated eosinophil counts, asthma and lung function; however, no association was found with any of these conditions (Wjst et al., 2009). Furthermore, SNP in the STAT4 in intron11, +90089T/C gene was found to be linked with the production of mite allergen-specific IgE in asthmatic Korean patients while no association of this SNP was also observed with asthma in Korean or Finnish populations (Park et al., 2005; Pykäläinen et al., 2005). In another study the same polymorphism was shown to be positively associated with asthma in a Chinese population (Li et al., 2007). An SNP in STAT6 rs324015 (2964G/A or c.*255A/G 3'UTR variant) was shown to be positively linked with mild atopic asthma in a Japanese population, but not with elevated serum IgE levels. In contrast, no association of this SNP was observed in a British population (Gao et al., 2000). Furthermore, SNPs in STAT6, rs324011 (6613C/T), was found to be associated with increased levels of serum IgE but no association was found between SNP 6613C/T and asthma (Kavalar et al., 2012).

Fork head family of transcription factors (FOX)—There is scant information available on FOX genes in relation to their association with lung-associated pathologies. The C>T allele at rs13217795 in FOXO3a was found to be associated with asthma in an Indian population. In fact, the risk for asthma development in a population with the CT allele was found to be 5.54 times higher and those with the CC genotype and 21.45 times higher than those with the TT allele (Barkund et al., 2015)

Retinoic acid receptor-related orphan receptor- α (ROR α)—ROR α belongs to the ROR subfamily of transcription factors, which have been identified in several mammalian species and are expressed in a tissue-specific manner (Zhang et al., 2015). ROR α is considered to be a master regulator of Th17 cell development and therefore plays an important role in the development of several autoimmune disorders and pulmonary diseases including COPD and pneumonia (Tsai et al., 2013). Distribution of rs8033552 (c. 272-19535C/T intron variant) in ROR α was found to differ significantly in COPD patients as compared to healthy controls. Specifically, allele A of rs8033552 was found to be associated with an increased risk of COPD whereas allele G may be associated with resistance to the disease. Odds Ratios (ORs) for genotypes AG vs GG were found to be 1.62, which increased to 2.69 in individuals with AA vs GG genotypes, showing the additive role of the A allele. Additionally, genotype AG and AA at rs8033552 were found to be significantly related to the increased risk of COPD in lower-BMI subjects as compared to GG genotype. Similarly, the GGAGATACA and GGAGATACG haplotypes were found to be significantly associated with an increased risk of COPD, whereas haplotypes GGAGATGTG and GGAGCTGTG exhibited a protective role in a Chinese population (Yuan et al., 2014) (Table 2). It has also been reported that *ROR- α* SNPs are a risk factor for asthma when present with a specific genotype of Neuropeptide S receptor 1 (*NPSR1*). The CC genotype in ROR α , rs7164773, is considered to be a risk factor for asthma only if the individual has one or two copies of the rare G allele of NPSR1 rs6972158 (Gln344Arg), whereas no association was shown in individuals homozygous for the *NPSR1* allele A (Acevedo et al., 2013).

3. Cytokines and chemokines

Following exposure of an organism to PAMPs and DAMPs, the primary physical manifestation of inflammation is the recruitment of immune cells. This process is controlled by cytokines and chemokines, which are critical modulators of acute and chronic inflammation. More than one hundred cytokines have been described to date each with varied functions and origins. Cytokines can be pro- or anti-inflammatory, mitogenic, hematopoietic and chemotactic (chemokines), and play important role in controlling all phases of inflammatory/immune responses. In the following section we will cover the studies demonstrating the association of cytokine and chemokine gene variants with pulmonary complications.

Tumor necrosis factor (TNF)—TNF plays a vital role in regulating inflammatory responses against a wide variety of stimuli. TNF represents two homologous proteins, TNF- α , which is primarily derived from mononuclear phagocytes, and TNF- β , derived from lymphocytes (Adkinson Jr et al., 2013). Both cytokines are only active when present in their homotrimeric (composed of three identical units of polypeptide) form. Lipopolysaccharide is one of the strongest inducer of TNF production (Lagoumintzis et al., 2008). Genetic variations present in the regulatory region of the *TNF* may affect circulating levels of TNF and may influence vulnerability to disease. A polymorphic association study was performed in a Taiwanese population with lung cancer comparing two genotypes of the *TNF- α* , rs1800629 (-308G/A, upstream variant c.-488A/G) AAGA and rs361525 (-238G/A) AA/GA. Patients with the AA/GA genotype at rs1800629 or GG genotype at rs362525 exhibited an

increased tendency to develop lung cancer (Shih et al., 2006) (Table 4). While SNPs rs1800629 (-308G/A), rs361525 (-238G/A or c.-418G/A) and rs1800630 (-863C/A) of *TNF* showed no association with TB susceptibility. SNP rs1799724 (-857C/T), on the contrary, showed an increased association with TB disease in an Asian population (Zhang et al., 2012b; Zhu et al., 2012) (Table 1). Asthma is a complex polygenic disease and *TNF-α* is believed to be one of the most important molecules involved in its pathogenic outcome. An SNP rs1800629 present in the promoter region of *TNF-α* was found to be positively associated with increased clinical pathology of asthma and this association was stronger in patients with a family history of acute asthma and in those of European-American ethnicity (Moffatt and Cookson, 1997; Qidwai and Khan, 2011; Witte et al., 2002). In another study performed on Caucasian French Canadian populations, genetic variants in *TNF-α* were found to be associated with diisocyanate-induced asthma. SNPs in prostaglandin-endoperoxide synthase-1 (*PTGS1*), rs5788 (+644C/A or c.639C/A); and transforming growth factor beta-1 (*TGFβ-1*), rs1800469 (-509C/T or -1347 C/T or c.*309T>C) showed an association with resistance to the disease whereas SNP rs1800629 in *TNF-α* and the *PTGS2* rs20417 (-765G/C or -899G/C) variant were found to be coupled with increased risk of diisocyanate-induced asthma (Yucesoy et al., 2016) (Table 3).

Interleukin-1 (IL-1)—The IL-1 family of cytokines includes IL1α, IL1β and the IL-1 receptor antagonist (IL1ra) (Bresnihan, 1999). IL1β is a pro-inflammatory cytokine that mediates both acute and chronic inflammation (Bird et al., 2002). Many SNPs identified in *IL1β* are believed to play important roles in lung disease. For example, SNPs rs16944 (-511C/T) and rs1143627 (-31T/C) were identified in promoter regions of IL1β (Drici et al., 2016) and smokers carrying the T allele at -31 and C allele at -511 positions exhibited an increased risk of lung cancer when smoking >30 packs per year. The risk of lung cancer was found to be particularly high in a Norwegian population homozygous for T/T at -31 and C/C at -511 positions (Zienolddiny et al., 2004). The *IL-1RN* (Interleukin 1 receptor antagonist) gene contains an 86 bp variable number tandem repeat (VNTR) polymorphism in intron 2, which is believed to have a significant role in non-small cell lung cancer when in the presence of the *IL1β-31T* allele (Lind et al., 2005) (Table 4). However, association of polymorphisms -511 C/T, -31 T/C of IL1β and VNTR of *IL-1RN* with regard to susceptibility to COPD are controversial. It was reported that these mutations have no effect on susceptibility to COPD in a study conducted on patients in Tokyo (Ishii et al., 2000), while a study performed on an East Asian population showed association of these mutations with increased risk for development of COPD (Xie et al., 2014). Additionally, the VNTR polymorphism in *IL-1RN-2* was found to be protective in the male population, while both *IL-1RN-1* and *IL-1RN-2* correlated with an increased risk of COPD in females (Shukla et al., 2012) (Table 2). Similar observations were recorded in Caucasian populations where the presence of these polymorphisms was assessed in asthma. In this study a polymorphism in *IL-1RA* (AA versus GG) was found to be a risk factor for asthma; however, the *IL-1β* -511C/T genotype was not linked with disease (He et al., 2015).

Interleukin-6 (IL-6)—IL-6 is primarily produced by mononuclear phagocytic cells; however, other cells including B and T lymphocytes, endothelial cells, hepatocytes, and bone marrow cells also produce this cytokine. IL-6 is an important factor in the maturation and

activation of B and T lymphocyte and thereby regulates immune responses and inflammation (Borish and Steinke, 2003). SNPs in the *IL-6* gene are associated with the progression of several diseases. For example, the SNP rs1800796 (-634C/G) shows a significant association with susceptibility to lung cancer in those patients homozygous for the C/C as compared to those homozygous for G/G or heterozygous (G/C) in an Asian population. However, no significant association was found for the *IL6* rs1800795 polymorphism (-174 G/C or c.-237C/G on *IL-6* transcript variant 1, and c.-274C/G in transcript variant 2) (Nie et al., 2014b). SNPs in *IL-6* have been also been shown to associate with changes in lung function parameters and asthma. It was also reported that the population carrying the -634 G allele having asthma/atopy were three times more susceptible to lung cancer as compared to the normal population carrying G allele and those with the CC genotype in non-smoking Chinese women (Seow et al., 2006). Of the three SNPs rs1800797 (-597G/A or c.-661A/G in transcript 1 and c.-698A/G in transcript 2), rs1800795 (-174 G/C) and rs1800796 (-572G/C or c.-636G/C in transcript 1 and c.-673G/C in transcript 2) identified in the promoter region of the *IL-6*, -597/G and -572/C were found to be associated with COPD in a Spanish population, while the -174C allele was linked to the rapid decline in lung function in a non-Hispanic, white population (Córdoba-Lanús et al., 2008; He et al., 2009) (Table 2).

Interleukin-17 (IL-17)—IL-17 is a pro-inflammatory cytokine secreted by T helper (Th17) cells. It plays significant roles in regulating both adaptive as well as innate immunity. Genetic polymorphisms in IL-17 have been interconnected with several immunopathologies (Onishi and Gaffen, 2010). The association of three SNPs in the *IL-17A* and *IL-17F* genes with lung cancer, rs2275913 (-152 G/A) of *IL-17A*, rs763780 (7488A/G or c.482A/G), and rs2397084 (7383A/G) of *IL-17F* has been reported in Tunisian populations. While a significant association of the *IL-17F* 7488 G allele with lung cancer was observed, individuals with the *IL-17F* 7488 A/G genotype showed a much higher risk for the disease. It was also suggested in this study that the *IL-17F* 7488 G allele enhances the risk of lung cancer amongst men and elderly individuals. In contrast, SNPs in *IL-17F* (7383 A/G) and *IL-17A* (-152G/A) were not found to be associated with disease (Kaabachi et al., 2014). In another study, the importance of *IL-17A* genetic polymorphisms rs142078089 (-420A/G) and rs17879568 (-73G/A) on susceptibility to NSCLC was investigated. It was observed that individuals carrying -73G/A or A/A genotypes and expressing high levels of IL-17 in peripheral blood mononuclear cells had a 2.09 or 2.52-fold increased chance, respectively, for development of NSCLC as compared to those with the -73GG genotype. SNP -420A/G in *IL17A* does not show any correlation with NSCLC (Ma et al., 2015). Genetic polymorphisms in *IL17A* rs2275913 (-197 G/A) and in *IL17F* (7488A/G and 7383A/G) have also been shown to be associated with asthma. Amongst these, genetic variants *IL-17A* -197G/A and *IL-17F* 7383A/G were found to be associated with childhood asthma in Tunisian populations, whereas the *IL-17F* 7488A/G polymorphism was not (Maalmi et al., 2014). Association of asthma with genetic polymorphism was also investigated for five *IL-17* related SNPs in Saudi populations, rs17880588 (G/A) and rs17878530 (C/T) in *IL17A* and rs763780 (T/C), rs11465553 (T/C), and rs2397084 (G/A) in *IL17F*. Of these variants only (rs17880588) G/A showed a significant association with asthma (Bazzi et al., 2011) (Table 3). In addition, a link between genetic polymorphisms in IL-17 and COPD has not yet been established.

Interleukin 8 (IL-8)—IL-8, also known as CXCL-8, is a pro-inflammatory chemokine that regulates the initiation of inflammation and plays an intermediate role in the activation and migration of neutrophils from peripheral blood into tissues. Genetic variations in the gene encoding IL-8 play important role in the outcome of several pulmonary diseases. An association between the IL-8 upstream variant rs4073 (-351A/T also known as -251A/T) and lung cancer has been reported, where allele A showed a significant increase in susceptibility in Asian populations, while no significant association was established with European or African populations (Gao et al., 2014). In another study, SNPs rs4073 (-251A/T) and rs2227306 (+781C/T or c.65-204C>T) of *IL-8* were reported to have association with susceptibility to NSCLC in Tunisian patients. Specifically, the 251T/T and +781C alleles were found to have significant association with tumor size and higher NSCLC stage compared to healthy controls. In both genotypes, mRNA expression of IL-8 was high, indicating its importance in susceptibility to lung cancer (Rafrafi et al., 2013) (Table 4). The association of *IL-8* genetic polymorphisms with COPD and asthma has also been studied. The -351A/A genotype was found to be associated with increased risk of COPD. Surprisingly, there is a five-fold increase in the risk for COPD if an individual carries at least one variant at *IL-8*-351 in combination with another variant in Colony Stimulating Factor 2 (*CSF-2*) rs25882 (c.350T/C or Thr117Ile allele). This study also showed that *CSF-2* and *IL-8* play important roles in the development of pathological symptoms of COPD in individuals exposed to indoor smoky coal emissions in a Chinese population (Shen et al., 2008). Another association study was also performed to assess the relationship of the -251A/T polymorphism within the promoter region of *IL-8* and COPD, and no significant association was found (Arinir et al., 2005). In contrast, this allele was found to be associated with childhood asthma and atopic dermatitis in children (Heinzmann et al., 2004). Moreover, there was a significant association between rs2227306 (+781C/T) of *IL-8* and asthma (Puthothu et al., 2006)

Interleukin-18 (IL-18)—IL-18 is a cytokine that induces production of IFN- γ and regulates the immune response to tumors. Genetic polymorphisms in the promoter region of *IL18*, rs1946519 (-656G/T or transcript variant c.-887T/G), rs1946518 (-607C/A or transcript variant c.-838A/C), and rs 18723 8 (-137G/C or transcript variant c.-368G/C), have been extensively studied. In lung cancer patients, a significantly higher frequency of allele A was found at position -607, which correlated with a reduction in *IL-18* expression. Moreover, Iranian patients carrying the C/A genotype at position -607 had a 2.60-fold increased risk while those carrying the A/A genotype at the same position had 3.15-fold increased risk of lung cancer (Farjadfar et al., 2009) (Table 4). The *IL-18* promoter-specific polymorphisms -607C/A and -137G/C have also been studied in relation to COPD. The frequency of the *IL-18*-607 C allele was significantly higher in patients with COPD and was found to be associated with increased disease susceptibility and severity of airflow restriction in male smokers within the Chinese Han population, whereas no significant association between *IL-18* G/C genotype was observed with COPD (Wang et al., 2013). The synonymous variation in *IL-18* rs549908 (105A/C) has been investigated for its association with asthma in a Chinese population where patients carrying the C/C homozygous genotype at rs549908 were observed to have a higher risk of developing asthma than those carrying the *IL18* 105A/C genotype (Lee et al., 2008). The association of the -607C/A genotype in

the promoter region of *IL-18* with asthma has been assessed, and although the frequency of the -607AA genotype appeared to be higher in Egyptian asthmatic children, the association was not statically significant (Shaaban et al., 2014) (Table 3)

Transforming growth factor- β (TGF- β)—TGF- β is a family of peptides mainly produced by chondrocytes, monocytes, fibroblasts and some specific T cells, which regulate cell growth and have both stimulatory as well as inhibitory effects on cells (Bilezikian et al., 2008). In addition, IL10 and TGF- β are thought to reduce allergic inflammation by inhibiting the synthesis of IgE and mast cell proliferation (Hobbs et al., 1998). Polymorphism rs 1800470 (+869T/C or missense variation c.29C/T or Pro10Leu) in *TGF- β* is associated with reduced expression of TGF- β and susceptibility to lung cancer in Asian populations, whereas no significant association was found in Caucasian populations. Moreover, the rs1800470 polymorphism was also proposed as a risk factor for NSCLC (Fan et al., 2014), and two other SNPs, rs1800469(-509C/T or upstream variant c.-1347T/C) and rs1800470 (+869T/C), and their haplotypes were investigated for their association with lung cancer in Korean populations. It was observed that individuals carrying at least one -509T allele exhibited a significantly reduced susceptibility to adenocarcinoma (AC) and small cell carcinoma (SM) as compared to patients carrying the -509C/C genotype. Similarly patients carrying T/C and C/C genotypes at the +869 position were found to have a decreased risk of adenocarcinoma and small cell carcinoma as compared to those with the -509C/+869T haplotypes (Park et al., 2006). In a study on Japanese smokers, the association between the C509T genotype of *TGF- β* and survival of treated patients with advanced NSCLC has been investigated. Patients carrying the T/T genotype were found to have a reduced survival rate as compared to those with the C/T or C/C genotype. It was also proposed that the T/T genotype at position -509 may be an independent prognostic marker for poor survival of treated, advance NSCLC (Togashi et al., 2011) (Table 4). In addition, genetic polymorphisms in *TGF- β* have been studied for their association with susceptibility to COPD and asthma. An association of the rs1800469 (-509 C/T or -1347 C/T) genotype with asthma was found in Mexican populations (Wu et al., 2010), whereas the -509 polymorphism was not associated with risk of clinically-manifested atopic asthma and other allergies (Buckova et al., 2001). Another SNP, rs2241712 (-10807G/A), identified in the promoter region of the *TGF- β* gene was found to be associated with COPD and asthma, while the G/A genotype was found to be protective with respect to these diseases. In addition, the G allele at the -10807 position was reported to be associated with asthma, however this association was not significant (Xue-Xi et al., 2011)

Interferon gamma (IFN- γ)—IFN- γ is considered to be crucial for innate host defense against many infections. Studies have demonstrated associations of polymorphic variants of the interferon gamma (*IFN- γ*) gene with susceptibility to tuberculosis. For example, the *IFN- γ* SNP rs62559044 (+874A/T) was found to be significantly associated with tuberculosis in a South African population. Moreover, it was found that NF- κ B preferentially binds to the +874T allele, which is over-represented in healthy controls, further suggesting that this genetic variation might be an important factor in the development of tuberculosis in the South African population (Rossouw et al., 2003). Genetic polymorphisms in the IFN- γ receptor 1 (*IFN- γ RI*) gene, rs2234711 (-56C/T), have been

investigated for TB susceptibility in many populations with significant variability. Through subgroup analysis it was found that genetic variability in *IFN- γ R1* was associated with susceptibility to TB in Africans but not in Asian or Caucasian populations, whereas the intron 2 SNP in the *IFN- γ R2* rs2834213 (207-877A/G) was strongly associated with TB in Vietnamese population (Hijikata et al., 2012; Wang et al., 2014). Three *IFN- γ* SNPs, rs1861494, T/C (+2109), rs2069718 (+3234C/T) in intron 3, and rs2430561 (+874T/A) in intron 1, have been found to be strongly associated with tuberculosis in Han Taiwanese populations. A homozygous T/T allele of rs2069718 (+3234C/T), A/A of rs2430561 (+874A/T), and allele C carrier of rs1861494 T/C (+2109) were associated with increased risk for TB (Lee et al., 2015) (Table 1). The *IFN- γ* SNP rs2430561 (+874T/A or c. 115-483A/T), widely referred to as *IFN- γ +874T/A*, was extensively studied for association with tuberculosis in many populations, and it was found that the individuals carrying the T allele show an approximately 27% reduced risk of developing tuberculosis as compared to the A/A homozygous condition. Moreover, this decreased susceptibility was specifically observed in Asians, and not in Caucasians (Tian et al., 2011). The *IFN- γ* SNP +874T/A was also investigated for an association with COPD and the +874T and A/T alleles of *IFN- γ* were found to be protective, whereas +874 A/A allele was associated with an increased risk of developing COPD in Macedonian populations (Trajkov et al., 2009). The role of the +874A/A homozygous allele of *IFN- γ* was observed to correlate with susceptibility to asthma as compared to the A/T and T/T genotypes in Caucasian and Asian populations (Nie et al., 2014a). In addition, the *IFN- γ +874T/A* gene polymorphism in combination with the *IL10* rs1800896 (-1082A/G or c.-1117A/G) gene polymorphism was observed to be a contributing factor in susceptibility to atopic asthma in children from Saudi Arabia (Hussein et al., 2014) (Table 3).

Chemokine C-X-C motif ligand (CXCL)—The CXCL family of chemokines includes CXCL10 and CXCL12. CXCL10 is a small chemokine molecule also known as IFN- γ induced protein 10 (IP-10) encoded by the *CXCL10* gene in human. The presence of the rs56061981 (-135G/A) SNP in the promoter region of *CXCL10* has been studied for an association with tuberculosis in Chinese populations and the -135G/A allele showed a potentially protective role (Tang et al., 2009). For the *CXCL12* gene SNP rs1801157 (-801G/A), the presence of the A allele has been proposed to significantly associate with increased risk of breast and lung cancer among Asians, but not among Europeans. Further, it has been proposed that the presence of this A allele in the 3-UTR of *CXCL12* may exert a regulatory role by directly increasing expression of the *CXCL12* gene, or due to its being a target of a cis-acting factor that upregulates the expression of *CXCL12* (Gong et al., 2012).

Chemokine C-C motif ligand (CCL)—The CCL family of chemokines includes CCL5, CCL24, CCL26, and CCL11. CCL5 functions as a chemoattractant for blood monocytes and memory T helper cells and induces release of histamine from basophils, which then triggers eosinophils (Colobran et al., 2007). Polymorphisms in the promoter region of the *CCL5* gene, s2107538 (-403G/A) and rs2280788 (-28C/G), have been found to be associated with many allergic diseases, such as atopic asthma and allergic rhinitis (Colobran et al., 2007). CCL11 (eotaxin-1), CCL24 (eotaxin-2), and CCL26 (eotaxin-3) are also potent eosinophils chemoattractants. SNPs in *CCL11*, rs4795896 (-576C/T), rs16969415 (-426 C/T),

rs17809012 (-384A/G) in promoter region and 67G/A in the signal peptide (exon 1), have been found to be associated with asthma (Chang et al., 2005; Nakamura et al., 2001; Raby et al., 2006; Shin et al., 2003). Three SNPs, two in intron 1 (+179TC and +275C/T) and one in intron 2 (+1265A/G) of the *CCL24* gene also show correlation with symptoms of asthma (Min et al., 2005). In addition, a genetic polymorphism, +2497T/G, present in the 3' UTR region of *CCL26* was also found to be associated with increased susceptibility to asthma (Colobran et al., 2007) (Table 3). Another SNP identified in the *CCL2/MCP-1* gene rs1024611 (-2578A/G) was found to be associated with asymptomatic tuberculosis infection, while higher *CCL2* gene expression in plasma was linked with tuberculin skin test positivity and the G allele of *CCL2* was more frequently present in tuberculin skin test asymptomatic controls (Hussain et al., 2011).

Another study demonstrated that Zambian carriers of the *CCL2* rs1024611 (-2518A/G) genotype are 2.8-fold more susceptible to tuberculosis than those with the -2518A/A genotype (Buijtelts et al., 2008). Allele G of the -2518A/G *CCL2* SNP was also found to be significantly coupled with susceptibility to tuberculosis in Asians and Latin-Americans of Hispanic ancestry, whereas it was not associated with disease in Africans from Ghana and South Africa (Feng et al., 2012). *CCL5* gene polymorphisms -28C/G and -403G/A were also studied in different populations with tuberculosis. Allele G of -28C/G was more frequent in tuberculosis patients than in healthy individuals in Tunisian and Spanish populations; however, no association of this variant was found in individuals originating from India or China. Two additional *CCL5* SNPs, 403G/A and In1.1 T/C, were not related to disease symptoms in Sudanese populations. Genotype G of the -28C/G polymorphism did show increased promoter activity resulting in increased expression of *CCL5* protein, which was associated with increased susceptibility to tuberculosis (Mhmoud et al., 2013) (Table 1). The rs2282691 SNP in the *CCL1* gene was found to be significantly associated with AEs in male patients with COPD. Populations carrying the A allele were found to be at increased risk of AEs in COPD, whereas the T allele-carrying population was resistant to AEs in COPD (Takabatake et al., 2006). Three SNPs in the *CCL5* gene, -403G/A, -28C/G and 375T/C, were studied for association with COPD and only the -28G allele was found to be inversely associated with computed tomography (CT) score and functionally milder emphysema (Hizawa et al., 2008).

4. Other important genes

Epithelial cadherin (E-cadherin) is synthesized by the *CDH1* gene and localizes in the membranes of epithelial cells where it induces the adhesion of neighboring cells in order to form organized tissues. An SNP within the 3' UTR of the *CDH1* gene (54 locus C/T) was found to be associated with susceptibility to lung cancer in a Northern Chinese population. The odds ratio of lung cancer in smokers with this allele compared to non-smokers was found to be 3.3, which shows that smokers are at significantly high risk for development of lung cancer. Further, the frequency of the C allele in *CDH1* was significantly higher in NSCLC and other cancer patients, as compared to healthy individuals. These observations indicate that individuals with the homozygous C/C genotype are significantly more susceptible to lung cancer compared to individuals with T/T or T/C genotypes (Li et al., 2011). In another study, five SNPs were reported in *ADAM33* (a disintegrin and

metalloprotease domain) in Indian populations. Genotypes S2 (rs528557) G/C and ST+5 (rs597980) C/T of ADAM33 were significantly associated with asthma susceptibility while homozygous mutant genotypes and mutant alleles F+1(rs511898) G/A, ST+4 (rs44707) A/C and V4 (rs2787094) C/G were related to a significant increase in asthma risk (Awasthi et al., 2011). The A allele at position rs2280091 of the ADAM33 gene was coupled with an increase in eosinophil counts and increased hyper-responsiveness leading to increased risk of asthma as compared to C allele (Chiang et al., 2012). ADAM33 gene polymorphisms were also found to be associated with COPD as SNPs T2 (rs2280090), T1 (rs2280091), S1 (rs3918396), Q-1 (rs612709), F+1 (rs511898), and ST+5 (rs597980) were coupled with increased risk of COPD in Asian populations, while SNPs T2, Q-1 and ST+5 correlated with risk in European populations. In contrast, no association was found between SNPs V4 (rs2787094), T+1 (rs2280089), S2 (rs528557) and COPD in any of the populations studied (Zhou et al., 2015) (Table 2). Over-expression of epithelial cell adhesion molecule (EpCAM) has also been associated with a wide variety of human cancers, including NSCLC. A non-synonymous SNP, rs1126497, was significantly linked with NSCLC. It was found in this study that the C/C genotype is a risk factor for both survival and recurrence of NSCLC as compared to the C/T and T/T genotypes (Yang et al., 2014c). Endothelin-1 (ET-1) has been implicated in pathogenic outcome of COPD. An adenine insertion (+134 insA/delA) and G198T in the ET-1 gene plays an important role in susceptibility to COPD. Genotype T/T at G198T shows a protective effect, whereas +134 insA/delA was found to be associated with increased COPD susceptibility. It was also found that patients carrying the G/T genotype often develop mild or moderate COPD, as compared to patients carrying the G/G genotype (Sampsonas et al., 2010).

With regard to pulmonary diseases, pulmonary surfactant plays an important role in reducing surface tension at aqueous-air interface and in regulating innate immune responses (Akella and Deshpande, 2013; Kishore et al., 2006; van der Schans et al., 1999). Surfactant is a complex mixture of neutral lipids, phospholipids, and proteins. The primary surfactant proteins include SP-A, SP-B, SP-C, and SP-D (van der Schans et al., 1999) and surfactant proteins gene polymorphisms have been found associated with TB, lung cancer, COPD, and other infectious diseases. SNPs in the *SFTPA1* and *SFTPA2* genes encoding pulmonary surfactant protein A (SPA) were found to be associated with pulmonary tuberculosis in the Han population in China. The G allele of rs17886395, T allele of rs1965707 and haplotype CCAAC–CGCA in combination with *SFTPA1* and *SFTPA2* were found to be risk factors, while haplotype CGAAC (*SFTPA1*) – AGCC (*SFTPA2*) and TCGAT- ACCC were found to be protective for pulmonary tuberculosis (Yang et al., 2014a). In other study the T allele of rs1914663 in the *SFTPA* gene was found to associate with increased risk of TB, whereas the TC+TT genotype was found to be higher in PTB and non-severe TB, as compare to controls, in the Han Chinese population (Li et al., 2016) (Table 1). In contrast, exon polymorphism rs1130866 in *SFTPB* was significantly protective from COPD and an increase in forced expiratory volume (FEV) in the Chinese Han population (Yang et al., 2014b). Another report on a non-Hispanic white population showed significant association between SNP rs3024791 in the promoter region of surfactant protein B (*SFTPB*) with COPD exacerbation (Foreman et al., 2008) (Table 2). A polymorphism in *SFTPB* (gene encoding SP-A) has also been shown to be associated with COPD susceptibility in Mexican (Guo et al., 2001) and German

populations (Seifart et al., 2002), while SNP rs721917 (T→C) in surfactant protein D (*SFTPD*) has found to be associated with emphysema and lung cancer in the Japanese Population (Ishii et al., 2012). Understanding of these genetic factors in pulmonary diseases will also lead to more accurate information about non-genetic factors and serve as a means to tailor treatment strategies.

Conclusions

Exploration of the variations in DNA sequences of immune-related genes and their association with human health and diseases is a primary area of genomic research. SNPs, the most common type of sequence variations, may be assigned as prognostic and predictive biomarkers in subpopulations and may also be useful as indicators of effective therapeutic strategies in specific allele carrying populations. The genome-wide association study approach has revealed many susceptible loci in the genome that are associated with disease risks. Since the association of SNPs with diseases varies for different subpopulations, these assessments are both interesting and challenging for researchers as the outcome may also be affected by the relationship between polymorphic markers on the chromosome (linkage disequilibrium) and the SNPs. Although, studies on SNPs provide answers to several lingering questions regarding the disease susceptibility and novel genetic pathways and networks that may influence and predict these diseases, taking into account other factors including locus and allelic heterogeneity in these studies will significantly improve the interpretation of results. Interestingly, these studies may reveal not only host-specific targets, but also targets present within pathogens. Nevertheless, SNP based research is still challenging due to identification of oncogenic genetic abnormalities from genetic and epigenetic noise. Identification of SNPs that contribute a large amount of risk to small number of patient will be a better approach than capturing only common SNPs which may contribute small amount of risk in a given population. (Shelling, 2009) To summarize, the use of cutting-edge sequencing and bioinformatics technology has set the stage to increase understanding of the genetics and evolution of pulmonary diseases.

Acknowledgments

This work was supported by Young Clinical Scientist Award from the Flight Attendant Medical Research Institute (FAMRI- 123253_YCSA_Faculty); NIH R15 (7 R15 ES023151 02); Southern University Foundation Grant (COS0016); and LBRN Startup Grant (2P20GM103424-14 -Subaward No. 100011) to SB.

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Figure 1. Schematic diagram representing a general mechanism of SNP mediated regulation of gene function

The expression of a gene is tightly regulated from the promoter region. Sequence of promoter region recognized by transcription factor, enhancer or suppressor molecules for optimal activation. Any variation in the promoter region sequence may lead to defective binding of transcription factor/enhancer/suppressor which may lead to no-, hypo-, or hyper-transcription. **A.** Normal (wild type) regulatory region of the gene and their transcription factor/suppressor and enhancers. **B.** SNP in the promoter region. **C.** Mutated transcription factor/enhancer/suppressor. Mutation in the Exon region may also lead to mutated protein. **D.** Normal PAMP receptors. **E.** Mutated receptor with less binding affinity for PAMPs. **F.** Mutated receptor with no binding ability for PAMPs. Figure also demonstrates the regulation of immune responses which involve recognition of cytokines and chemokines by their receptors. Any change in this interaction may lead to reduced or hyper immune response as demonstrate in: **G.** WT-Receptor/WT-Cytokines & Chemokines. **H.** WT-Receptor/Mutated Cytokines & Chemokines and **I.** Mutated receptor/normal cytokines & Chemokines.

Table 1

SNPs associated with TB disease

S. No	SNPs	Gene	Disease	Impact	Odd Ratio	Population	Reference
SNPs in Pattern Recognition Receptors							
1	G allele of SNP rs5743618	<i>TLR1</i>	Tuberculosis Han Chinese children.	Coupled with increased risk	OR=2.40, 95% CI(1.41-4.07)	Han Chinese from North China	(Qi et al., 2015)
2	Homozygous C/C genotype at position rs3804100	<i>TLR2</i>	Latent tuberculosis	Coupled with increased risk	OR = 2.262, 95% CI(1.433-3.570)	Chinese population	(Wu et al., 2015)
3	G/A genotype of SNP rs5743708	<i>TLR2</i>	Pulmonary tuberculosis	Significantly high	OR = 6.087, 95% CI(1.687-21.968)	Chinese population	(Wu et al., 2015)
4	G/G genotype at rs7873784	<i>TLR4</i>	TB patient	Significantly high	OR = 2.136, 95% CI(1.312-3.478)	Chinese population	(Wu et al., 2015)
5	C/C genotype at position rs3764879	<i>TLR8</i>	TB patient	Significantly high	OR= 1.982, 95% CI(1.292-3.042)	Chinese population	(Wu et al., 2015)
6	Allele G of rs352139 (A>G)	Intronic region of <i>TLR9</i>	Tuberculosis	Protective role	Under the recessive model (A/G + A/A vs G/G) OR= 2.37	Mexican population	(Torres-García et al., 2013)
7	Allele A of rs352139 (A>G)	Intronic region of <i>TLR9</i>	Tuberculosis	Significantly increased risk	OR = 1.75, (AA vs AG+GG in Indonesian female group) OR = 1.827	Mexican population and Indonesian female	(Torres-García et al., 2013), (Lagoumintzis et al., 2008)
8	Pro268 to Ser (rs2066842)	<i>NOD2</i>	Tuberculosis	Resistance	OR = 0.55, 95% CI(0.32-0.94)	African American	(Austin et al., 2008)
9	Arg702 to Trp (rs2066844)	<i>NOD2</i>	Tuberculosis	Resistance	OR = 0.27, 95% CI(0.08-0.88),	African American	(Austin et al., 2008)
10	Ala725 to Gly (rs5743278)	<i>NOD2</i>	Tuberculosis	Susceptibility	OR = 2.16, 95% CI(1.10-4.72)	African American	(Austin et al., 2008)
11	rs69287125 and rs137824326 allele G for both SNPs	<i>MBL</i>	Pulmonary tuberculosis	protective	NA	Chinese population	(Bing et al., 2012)
12	rs69287125 and rs137824326 allele A for both SNPs	<i>MBL</i>	Pulmonary tuberculosis	Coupled with increased risk	NA	Chinese population	(Bing et al., 2012)
13	(rs34039386) G1186A	<i>MRC1</i>	Tuberculosis	higher in susceptible group	OR = 0.76, 95% CI(0.58-0.98)	Chinese population	(Zhang et al., 2012a)
SNPs associated with Cytokines/Chemokines							

S. No	SNPs	Gene	Disease	Impact	Odd Ratio	Population	Reference
14	rs1799724 found near TNF gene, 857C>T, CC+CT vs. TT	TNF	Tuberculosis	Increased association	OR 2.13, 95% CI(1.25–3.63)	Asian population	(Zhang et al., 2012b; Zhu et al., 2012)
15	(rs62559044) 874T	IFN- γ	Tuberculosis	significantly associated	OR=1.64, 95% CI(1.16–2.30)	South African population	(Rossouw et al., 2003)
16	CC+CT vs TT allele of rs2069718	IFN- γ	Tuberculosis	risk factor	OR=2.83, 95% CI(1.89, 4.25)	Han Taiwanese populations	(Lee et al., 2015)
17	TT+AT vs AA homozygous rs2430561	IFN- γ	Tuberculosis	susceptibility	OR=3.44, 95% CI(1.10, 10.74)	Han Taiwanese populations	(Lee et al., 2015)
18	GG vs AA+ AG rs1861494	IFN- γ	Tuberculosis	susceptibility	OR=5.74, 95% CI(2.61, 12.64)	Han Taiwanese populations	(Lee et al., 2015)
19	(rs2430561) 874TT+TA as compared to AA genotype	IFN- γ	Tuberculosis	27% reduced risk	OR = 0.71, 95% CI(0.52–0.97)	Asians, but not in Caucasians	(Tian et al., 2011)
20	(rs2234711) 56 CC+TC vs. TT	IFN- γ R1	Tuberculosis	associated with susceptibility	OR = 1.24, 95% CI(1.02–1.51)	Africans but not in Asian or Caucasian populations	(Wang et al., 2013)
21	rs2834213	IFN- γ R2	Tuberculosis	strongly associated	OR=0.69, 95% CI(0.52–0.91)	Vietnamese	(Hijikata et al., 2012)
22	2518A/G genotype	CCL-2	Tuberculosis	2.8 fold more susceptible	OR=2.8, 95% CI (1.4–5.8)	Zambian populations	(Buijtelts et al., 2008)
23	(rs1024611) 2518 G	CCL-2	Tuberculosis	coupled with susceptibility	OR=1.51, 95% CI(1.11–2.04)	Asians and Latin-Americans of Hispanic ancestry	(Feng et al., 2012)
24	28 C/G	CCL5	Tuberculosis	more frequent in tuberculosis patients	OR=0.24, 95% CI(0.08–0.73)	Tunisia and Spain populations	(Mhmoud et al., 2013)
25	(rs56061981) 135G>A, AA or AG	CXCL10	Tuberculosis	Potential protective role	OR=0.51, 95% CI(0.29 – 0.91)	Chinese populations	(Tang et al., 2009)
SNPs associated with other important genes							
26	G allele of rs17886395	SFTPA2	Pulmonary tuberculosis	Risk factors	OR=1.792, 95% CI(1.318–2.439)	Han population in China	(Yang et al., 2014)
27	T allele of rs1965707	SFTPA2	Pulmonary tuberculosis	Risk factors	OR=1.425, 95% CI(1.006–2.016)	Han population in China	(Yang et al., 2014)
28	T allele of rs1914663	SFTPA	Tuberculosis	Increased risk	OR=1.42, 95% CI(1.10–1.81)	Han Chinese population	(Li et al., 2016)

Table 2

SNPs associated with COPD

S. No	SNPs	Gene	Disease	Impact	Odds Ratio	Population	Reference
SNPs in Pattern Recognition Receptors							
1	T399I	<i>TLR4</i>	COPD	2.4 fold increased risk	OR=2.4, 95% CI(1.02–5.64)	Greek smoker patients	(Speletas et al., 2010)
2	C allele at position T1486C	Promoter region of <i>TLR-9</i>	COPD	Significantly high	NA	Germany	(Pabst et al., 2013)
3	A/T rs1077861	<i>NOD2</i>	COPD	development and progression	NA	Japanese population	(Kinose et al., 2012)
SNPs in Transcription Factors							
4	NF- κ B1:- 94del>insATTG	<i>NF-κB</i>	COPD	Susceptibility	OR=1.27, 95% CI(1.06–1.52)	Southern Chinese population	(Huang et al., 2013)
5	Arg/Arg or Arg/ser at codon 31, rs1801270	p21	COPD	Susceptibility	OR = 2.07, 95% CI(1.06–4.05)	Taiwan Chinese patients	(Lee et al., 2006)
6	AG or AA of rs803352	ROR α	COPD	Coupled with increased risk	OR=1.62, 95% CI(1.17–2.26)	Chinese population	(Yuan et al., 2014)
7	haplotypes GGAGATGTG and GGAGCTGTG	ROR α	COPD	protective role	NA	Chinese population	(Yuan et al., 2014)
SNPs in Cytokines/Chemokines							
8	T allele 511 and C allele 31 of IL-1 β and VNTR polymorphism of <i>IL-1RN</i>	<i>IL-1β</i> , VNTR polymorphism of <i>IL-1RN</i>	COPD	Coupled with increased risk	OR=1.61, 95% CI(1.13–2.31) OR=1.55, 95% CI(1.14–2.11) and VNTR OR=3.20, 95% CI(1.13–9.12)	East Asian population	(Xie et al., 2014)
9	VNTR polymorphism	<i>IL-1RN-2</i>	COPD	protective	NA	Caucasian male populations	(Shukla et al., 2012)
10	VNTR polymorphism	<i>IL-1RN-2</i>	COPD	Coupled with increased risk	OR=2.28, 95% CI(1.03–5.08)	Caucasian female populations	(Shukla et al., 2012)
11	597/G (rs1800797) and 572/C (rs1800796)	<i>IL-6</i>	COPD	associated	OR=1.17 95% CI(0.71–1.92) and OR=0.30 95% CI(0.12–0.79)	Spanish Population	(Córdoba-Landis et al., 2008; He et al., 2009)
12	351AA	<i>IL-8</i>	COPD	Coupled with increased risk	OR=2.71, 95% CI(1.04–7.04)	Chinese population	(Shen et al., 2008)
13	351A/A + CSF2 (rs25882) Thr117Il	<i>IL-8</i>	COPD	the risk to COPD increases by five-fold	OR=5.14, 95% CI(1.32–29.86)	Chinese population	(Shen et al., 2008)

S. No	SNPs	Gene	Disease	Impact	Odds Ratio	Population	Reference
14	(rs1946518) 607 C	<i>IL-18</i>	COPD	Associated with the increase in disease susceptibility	OR=1.48, 95% CI(1.01–2.15)	Chinese Han male smokers population	(Wang et al., 2013)
15	(rs2430561) 874T and A/T	<i>IFN-γ</i>	COPD	protective	OR=0.260, 95% CI(0.157–0.431)	Macedonian populations	(Trajkov et al., 2009)
16	(rs2430561) 874 A/A	<i>IFN-γ</i>	COPD	Coupled with increased risk	OR=9.154, 95% CI(4.507–18.591)	Macedonian populations	(Trajkov et al., 2009)
17	AA+AT vs. TT allele rs2282691	<i>CCL1</i>	Acute exacerbations (AEs) in COPD	significantly associated	OR=2.82 95% CI(1.39–5.71)	Japanese patients with COPD	(Takabatake et al., 2006)
SNPs associated with other important genes							
18	T2 (rs2280090), T1 (rs2280091), S1 (rs3918396), Q-1 (rs612709), F+1 (rs511898) and ST+5 (rs597980)	<i>ADAM33</i>	COPD	were coupled with increased risk	OR = 0.443, 95% CI (0.310–0.632), OR = 2.243, 95 % CI(1.391–3.617), OR=1.727, 95 % CI(1.214–2.459)OR=0.581, 95 % CI(0.363–0.928), OR=1.321, 95% CI(1.000–1.745), no data were available from Asian populations;,,	Asian populations	(Zhou et al., 2015)
19	T2 (rs2280090), Q-1 (rs612709) ST+5 (rs597980)	<i>ADAM33</i>	COPD	were coupled with increased risk	OR=2.289, 95% CI(1.112–4.710), OR=0.552, 95% CI(0.440–0.692) OR=1.379, 95% CI(1.057–1.799)	European populations	(Zhou et al., 2015)
20	T/T at G198T	<i>ET-1</i>	COPD	protective effect	OR = 0.164, 95%, CI(0.044–0.602)	Smoker COPD patients	(Sampsonas et al., 2010)
21	GG genotype compare to GT/TT genotype in G198T	<i>ET-1</i>	COPD	Increased COPD	OR = 1.241, 95% CI(0.982–1.568)	Smoker COPD patients	(Sampsonas et al., 2010)
22	rs3024791	<i>SFTPB</i>	COPD	Susceptibility	OR=0.6 95% CI(0.4–0.9)	non-Hispanic white population	(Foreman et al., 2008)

Table 3

SNPs associated with Asthma.

S. No	SNPs	Gene	Disease	Impact	Odds Ratio	Population	Reference
SNPs in Pattern Recognition Receptors							
1	T/T homozygous genotype of rs7656411	<i>TLR2</i>	Asthma	Significant lower risk	OR = 0.63, 95% CI(0.41-0.98)	Chinese population	(Qian et al., 2010)
2	T allele at SNPs 1196T (Thr399Ile)	<i>TLR4</i>	Asthma	Resistant	OR = 0.70, 95% CI(0.49-0.99)	North Indian population	(Sinha et al., 2014)
3	Allele T at position rs2381289	<i>TLR6</i>	allergic rhinitis in asthma	Positively associated	OR=1.79, 95% CI(1.10-2.91)	Chinese population	(Qian et al., 2010)
4	Allele A at position rs11466651	<i>TLR10</i>	Allergic rhinitis	Negatively associated	OR=0.49, 95% CI(0.26-0.95)	Chinese population	(Qian et al., 2010)
5	rs2066844 (Arg702Trp), G2722C	<i>NOD2</i>	Allergic rhinitis	3-fold risk	OR=3.16, 95% CI(1.74-5.76)	School children Germany	(Kabesch et al., 2003)
6	rs2066844 (Arg702Trp), G2722C	<i>NOD2</i>	Atopic dermatitis	2-fold risk	OR=1.85, 95% CI(1.10-3.13)	School children Germany	(Kabesch et al., 2003)
7	rs869147565 (Leu1007Pro), C3020	<i>NOD2</i>	Atopy	50% increased susceptibility	OR= 1.49, 95% CI(1.02-2.18)	School children Germany	(Kabesch et al., 2003)
8	T allele rs1077861	<i>NOD2</i>	Asthma	Decreased risk	OR=0.648, 95% CI(0.461-0.911)	Caucasian adult population	(Weidinger et al., 2005)
9	A allele at rs3135500	<i>NOD2</i>	Asthma	Coupled with increased risk	OR = 1.374, 95% CI (1.045-1.809)	Caucasian adult population	(Weidinger et al., 2005)
10	A allele at rs743266	<i>NOD2</i>	Allergic rhino conjunctivitis	Decreased risk	OR=0.820, 95% CI(0.672-0.998)	Caucasian adult population	(Weidinger et al., 2005)
11	T allele at rs2066842	<i>NOD2</i>	Allergic rhino conjunctivitis	Decreased risk	OR=0.801, 95% CI(0.600-0.973)	Caucasian adult population	(Weidinger et al., 2005)
12	16974 C/T (rs4612666)	<i>NLRP3</i>	Asprin intolerance asthma	Significantly associated	OR= 1.81, 95% CI(1.27-2.56)	Kanagawa, Japan	(Hitomi et al., 2009)
13	A in MBL2 codon54	<i>MBL</i>	Asthma	significantly associated	OR=1.9, 95% CI(1.4-2.4)	North Indian populations	(Birbhan et al., 2012)
14	1011 G/A allele G + 341 T/C allele C	<i>MBL + SP-D</i>	Allergic rhinitis, asthma and Allergic Bronchopulmonary Aspergillosis (ABPA)	significantly associated	OR=3.8571, OR=2.33	Indian populations	(Kaur et al., 2006; Suman

S. No	SNPs	Gene	Disease	Impact	Odds Ratio	Population	Reference
SNPs in Transcription Factors							
15	SNPs rs2306581, rs957971, and rs1026916	<i>STAT3</i>	Asthmatic adults and children	strongly associated with reduced lung function	NA	asthmatic adults and children	(Litonjua et al., 2005)
16	T90089C	<i>STAT4</i>	asthmatic linked with the production of mite allergen-specific IgE	linked with the production of mite allergen-specific IgE	OR=1.38, 95% CI(1.03-1.86)	Korean or Finnish populations	(Park et al., 2005; Pykalainen et al., 2005)
17	T90089C	<i>STAT4</i>	Asthma	positively associated	OR=1.39, 95% CI(0.74-2.60)	Chinese population	(Li et al., 2007)
18	(rs324015) G2964A	<i>STAT6</i>	Asthma	positively linked	OR=3.19, 95% CI(1.40-7.08)	Japanese population but not in British population	(Gao et al., 2000)
19	Allele C/T (rs13217795)	<i>FOXO3a</i>	Asthma	CT allele have 5.54 times higher risk and TT allele have 21.45 times higher risk	OR=5.54, 95% CI(2.48 to 12.62)	Indian population	(Barkund et al., 2015)
20	CC genotype rs7164773+G rs6972158	<i>ROR-α +NPSRI</i>	Asthma	risk factor	OR=2.0, 95% CI(1.36–2.93) in BAMSE; and OR= 1.61, 95% CI(1.18–2.19)	European population	(Acevedo et al., 2013)
SNPs associated with Cytokines/Chemokines							
21	308 G/A, rs1800629	<i>TNF</i>	Asthma	Positively associated with clinical pathology	OR=3.16, 95% CI(1.04–9.66)	European– American ethnicity	(Moffatt and Cookson, 1997; Oidwai and Khan, 2011; Witte et al., 2002)
22	rs5788 (c.639C>A+ c.*309T>C (rs1800469)	<i>PTGS1+TNF</i>	Di-isocyanate induced asthma	Resistance	OR = 0.38, 95% CI(0.17, 0.89) and OR = 0.38, 95% CI(0.18-0.74)	Caucasian French Canadian populations	(Yucesoy et al., 2016)
23	rs20417+ rs1800629	<i>PTGS2+TNF</i>	Di-isocyanate induced asthma	Increased risk	OR = 6.40, 95% CI(1.06– 38.75) and OR = 2.08, 95% CI(1.03-4.17)	Caucasian French Canadian populations	(Yucesoy et al., 2016)
24	IL-1RA polymorphism	<i>IL-1R</i>	Asthma	Coupled with increased risk	homozygote model OR=1.32, 95% CI(1.12-1.56), recessive model: OR=1.39, 95% CI(1.18-1.63)	Caucasian populations	(He et al., 2015)
25	(rs2227306) 781C/T	<i>IL-8</i>	Asthma	significant association	NA	South-Western part of Germany	(Puthothu et al., 2006)

S. No	SNPs	Gene	Disease	Impact	Odds Ratio	Population	Reference
26	(rs2275913) 197G	<i>IL-17A</i>	Childhood asthma	associated	OR = 1.89, 95% CI(1.21– 2.97)	Tunisia populations	(Maalmi et al., 2014)
27	7383A/G	<i>IL-17F</i>	Childhood asthma	associated	OR =2.93, 95% CI(1.39–6.31)	Tunisia populations	(Maalmi et al., 2014)
28	(rs17880588) G/A	<i>IL-17F</i>	Asthma	significant association		Saudi populations	(Bazzi et al., 2011)
29	(rs549908) 105 AA	<i>IL-18</i>	Asthma	Higher risk of developing	OR=3.019, 95% CI(1.635–5.576).	Chinese population	(Lee et al., 2008)
30	(rs1946518) 607AA and CA	<i>IL-18</i>	Asthma	Higher in asthma patients	OR=1.28, 95 % CI(0.38–4.2)	Egyptian population	(Shaaban et al., 2014)
31	T and TT allele of C-509T (rs1800469)	<i>TGF-β</i>	Asthma	increased risk of asthma	OR=1.42, 95% CI(1.08–1.87) and OR=1.95, 95% CI(1.36–2.78)	Mexican populations	(Wu et al., 2010)
32	10807 G	<i>TGF-β</i>	Asthma	protective to the disease	NA		(Xue-Xi et al., 2011)
33	(rs2430561) 874 AA vs AT + TT	<i>IFN-γ</i>	Asthma	susceptibility	OR=1.42, 95% CI(1.04–1.93) and Asians OR=2.52, 95% CI(1.49–4.25)	Caucasian and Asian populations	(Nie et al., 2014)
34	(rs2430561) 874 T/A+ (rs1800896) 1082A/G	<i>IFN-γ +IL-10</i>	Atopic asthma	susceptibility	NA	Saudi Arabia	(Hussein et al., 2014)
35	403G/A and 28C/G	<i>CCL5</i>	Asthma atopy and allergic rhinitis	associated	NA	-	(Colobran et al., 2007)
36	rs4795896) 576C/T, (rs16969415) 426C/T, (rs17809012) 384 A/G in promoter region	<i>CCL11</i>	Asthma	associated	NA	-	(Chang et al., 2005; Nakamura et al., 2001; Raby et al., 2006; Shin et al., 2003)
37	(rs374458) 67G/A	<i>CCL11</i>	Asthma	associated	NA	-	(Chang et al., 2005; Nakamura et al., 2001; Raby et al., 2006; Shin et al., 2003)
38	179T/C, 1265A/G and 275C/T	<i>CCL24</i>	Asthma symptoms	show correlation	NA	-	(Min et al., 2005)

S. No	SNPs	Gene	Disease	Impact	Odds Ratio	Population	Reference
39	2497T/G	CCL26	Asthma	increased susceptibility	NA	-	(Colobran et al., 2007)
SNPs associated with other important genes							
40	(rs528557) GG vs GC and CC	ADAM33	Asthma	significantly associated	OR=6.66, 95% CI(3.58–12.42) and OR=30.86, 95% CI(14.44–65.94)	Indian populations	(Awasthi et al., 2011)
41	ST+5 (rs597980) CC vs CT and TT	ADAM33	Asthma	significantly associated susceptibility	OR=1.78, 95% CI(0.97-3.25) and OR=3.12, 95% CI(1.65-5.92)	Indian populations	(Awasthi et al., 2011)
42	F+1(rs511898) G/A, ST+4 (rs44707) A/C and V4 (rs2787094) C/G	ADAM33	Asthma	significant increase	OR=1.84, 95% CI(1.35-2.50) OR=1.39, 95% CI(1.03–1.90) 0.010, OR=1.38, 95% CI(1.02–1.88)	Indian populations	(Awasthi et al., 2011)
43	allele A of rs2280091	ADAM33	Asthma	increased hyper- responsiveness	OR= 1.9336, 95% CI=1.2064–3.0991	Taiwan	(Chiang et al., 2012)

Table 4

SNPs associated with Lung Cancer

S. No	SNPs	Gene	Disease	Impact	Odds Ratio	Population	Reference
SNPs in Transcription Factors							
1	1xBa. 2758AA	<i>IκBα</i>	Lung Cancer	Increased risk	OR=1.53, 95% CI(1.30–1.80)	Chinese populations	(Huang et al., 2013)
2	Pro/Pro or Pro/Arg at codon 72, rs1042522	<i>p53</i>	Lung Cancer	Susceptibility	OR=1.83, 95% CI(1.48–2.26)	Korean	(Piao et al., 2011)
3	TT genotype of rs3816769	<i>STAT3</i>	Lung cancer	Coupled with increased risk	OR=3.1, 95% CI(1.6–5.9)	Poland	(Domanska et al., 2013)
4	GG genotype of rs744166	<i>STAT3</i>	Lung cancer	Coupled with increased risk	OR = 2.60, 95%CI(1.36–4.96)	Poland	(Domanska et al., 2013)
5	minor allele of rs4796793, rs7211777, rs12949918, rs744166, rs9912773 and rs3869550	<i>STAT3</i>	NSCLC	decreased risk	OR = 0.68, 95% CI(0.51–0.92), OR = 0.67, 95% CI(0.50–0.90), OR = 0.73, 95% CI(0.54–0.97), OR = 0.69, 95% CI(0.51–0.92), OR = 0.75, 95% CI(0.55–0.98) and OR = 0.70, 95% CI(0.53–0.94)	China	(Jiang et al., 2011)
SNPs associated with Cytokines/Chemokines							
6	308 G>A, AA/GA genotype at rs1800629	<i>TNF</i>	Lung Cancer	Advancement of disease	OR=3.75, 95% CI(2.38–5.92)	Taiwanese population	(Shih et al., 2006)
7	AA/GA genotypes against GG genotype at rs361525 (238 G/A)	<i>TNF</i>	Lung Cancer	Increased tendency	OR=0.26, 95% CI(0.13–0.50)	Taiwanese population	(Shih et al., 2006)
8	–511 (C>T; dbSNP: rs16944), 511C/C	<i>ILβ</i>	Lung Cancer	increased risk	OR=2.51, 95% CI(1.47–4.58)	Norwegian population	(Zienoldiny et al., 2004)
9	–31 (T/C; dbSNP: rs1143627), –31T/T	<i>ILβ</i>	Lung Cancer	Coupled with increased risk	OR=2.39, 95% CI(1.29–4.44)	Norwegian population	(Zienoldiny et al., 2004)
10	86 bp VNTR in intron 2+31T in <i>ILβ</i>	<i>IL-1RN</i>	NSCLC	significant role	C/T OR=3.08, 95% CI(1.10–8.62) and T/T OR=5.87, 95% CI(2.15–16.05)	Norwegian	(Lind et al., 2005)
11	C/C homozygous, rs1800796, –634C/G	<i>IL-6</i>	Lung Cancer	susceptibility	OR=1.33, 95 % CI(1.20–1.47)	Asian population	(Nie et al., 2014)
12	634 G, (rs1800796) + asthma/atopy	<i>IL-6</i>	Lung Cancer	Three times more susceptible	OR=3.1, 95% CI(1.2–8.3)	Chinese women	(Seow et al., 2006)
13	(rs4073), c–352A>T, AA vs TT allele of 251A/T	<i>IL-8</i>	Lung cancer	significant increase in susceptibility	OR=1.64, 95% CI(1.06–2.52)	Asian populations	(Gao et al., 2014)

S. No	SNPs	Gene	Disease	Impact	Odds Ratio	Population	Reference
14	(rs4073) 251T/T as compare to AA genotype	<i>IL-8</i>	NSCLC	significant association	OR = 2.55, 95% CI(1.32– 4.95)	Tunisian patients	(Rafrafi et al., 2013)
15	(rs2227306) 781C	<i>IL-8</i>	large tumor size lung cancer	significant association	OR = 2.29	Tunisian patients	(Rafrafi et al., 2013)
16	(rs763780) 7488 G allele	<i>IL-17F</i>	Lung Cancer	Coupled with increased risk	OR = 1.84, 95% CI(1.04– 3.23)	Tunisian men	(Kaabachi et al., 2014)
17	73G/A or A/A (rs17879568) as compare to -73GG	<i>IL-17A</i>	NSCLC	2.09 or 2.52– times increased	OR= 2.09, 95% CI(1.46 – 2.98) OR = 2.52, 95% CI(1.30– 4.88)	Chinese population	(Ma et al., 2015)
18	(rs1946518) 607 CA and AA	<i>IL-18</i>	Lung cancer	2.60– fold, 3.15 fold increased risk	OR=2.60, 95% CI(1.26– 5.36) and OR=3.15, 95% CI(1.16– 8.55)	Iranian patients	(Farjadfar et al., 2009)
19	(rs1800470) 869T/C	<i>TGF-β</i>	Lung cancer	Susceptibility to lung cancer	OR=1.26, 95% CI(1.01– 1.57) and OR=1.04, 95% CI(0.60– 1.82)	Asian populations	(Fan et al., 2014)
20	(rs1800469), 509T as compare to CC genotype	<i>TGF-β</i>	Adenocarcinoma (AC) and small cell carcinoma	Significantly reduced susceptibility	OR= 0.63, 95% CI(0.42-0.96)	Korean populations	(Kang et al., 2006)
21	(rs1800470) 869TC + CC genotype as compare to TT genotype	<i>TGF-β</i>	Small cell carcinoma	Associated with decreased risk	OR=0.52, 95% CI(0.31-0.88)	Korean populations	(Kang et al., 2006)
22	(rs1800469), 509 (TT/CT or CC)	<i>TGF-β</i>	NSCLC	Reduced survival rate	OR=2.201, 95% CI(1.212-3.864)	Japanese patients	(Togashi et al., 2011)
23	(rs1801157) 801 GA/AA versus GG	<i>CXCL12</i>	Breast and lung cancer	Coupled with increased risk	OR=1.36, 95% CI(1.17-1.59)	Asians	(Gong et al., 2012)
SNPs associated with other important genes							
24	3' UTR 54T allele	<i>CDH1</i>	NSCLC	susceptibility	OR=0.68, 95% CI(0.49-0.92)	Northern Chinese population	(Li et al., 2011)
25	rs1126497 CT+TT genotype as compare to CC	<i>EpCAM</i>	NSCLC	risk factor for both survival and recurrence	OR=1.40, 95% CI(1.02-1.94) and recurrence OR=1.34, 95% CI(1.02-1.77)	Chinese Population	(Yang et al., 2014)
23	SNP rs721917 (T/C), Met11Thr	<i>SFTPD</i>	Lung cancer	Associated with	NA	Japanese Population	(Ishii et al., 2012)