Published in final edited form as:
Front Biosci. ; 17: 407–429.

Genetic variant associations of human SP-A and SP-D with acute and chronic lung injury

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Abstract

Pulmonary surfactant, a lipoprotein complex, maintains alveolar integrity and plays an important role in lung host defense, and control of inflammation. Altered inflammatory processes and surfactant dysfunction are well described events that occur in patients with acute or chronic lung disease that can develop secondary to a variety of insults. Genetic variants of surfactant proteins, including single nucleotide polymorphisms, haplotypes, and other genetic variations have been associated with acute and chronic lung disease throughout life in several populations and study groups. The hydrophilic surfactant proteins SP-A and SP-D, also known as collectins, in addition to their surfactant-related functions, are important innate immunity molecules as these, among others, exhibit the ability to bind and enhance clearance of a wide range of pathogens and allergens. This review focuses on published association studies of human surfactant proteins A and D genetic polymorphisms with respiratory, and non-respiratory diseases in adults, children, and newborns. The potential role of genetic variations in pulmonary disease or pathogenesis is discussed following an evaluation, and comparison of the available literature.

Keywords

SFTPA1; SFTPA2; SP-D; Polymorphism; Single Nucleotide; collectins; lung disease; review

2. INTRODUCTION

Disease susceptibility is influenced by a number of overlapping genetic and non genetic factors, most of which may have a different level of impact at different stages of life. Genetic components that determine susceptibility to acute and chronic lung disease have been studied within different biological contexts, and correlated with environmental factors, such as pollutants, concurrent diseases, or particular conditions such as prematurity or need for mechanical ventilation (1–11). For example, genetic variation in genes involved in pulmonary adaptation may contribute, under certain conditions, to differences in disease susceptibility, or disease severity among individuals. Study of the genetics of pulmonary surfactant components, and in particular of the surfactant proteins, have revealed correlation with lung disease in neonates, children, and adults (12–14). Genetic variations and mutations of the surfactant proteins have been correlated with disease susceptibility or pathogenesis (12). In the present review, we expand on the most recent review (12) and summarize associations of single nucleotide polymorphisms (SNPs), and genetic variants or haplotypes

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of the two innate immunity molecules, surfactant proteins A (SP-A) and D (SP-D), with neonatal, pediatric, and adult disease.

2.1. Pulmonary surfactant and surfactant proteins

Pulmonary surfactant, a lipoprotein complex, is synthesized by the alveolar epithelial type II cells in the lung, and its key function is to reduce the surface tension at the alveolar air-liquid interface, and consequently prevent alveolar collapse at low lung volumes. As a consequence of its surface tension lowering function, and the role of its components in innate immunity, pulmonary surfactant is not only essential for life, but is also critical for lung health, and normal lung function throughout life (14, 15). Pulmonary surfactant is composed by approximately 90% of lipids, and 10% of proteins. The lipid fraction is primarily composed by phospholipids, most of which is phosphatidylcholine (PC) and dipalmitoylphosphatidylcholine (DPPC) in particular, a key component involved in the reduction of surface tension. The second most abundant phospholipid is phosphatidylglycerol (PG), and the remainder consists of phosphatidylethanolamine (PE), phosphatidylSerine (PS), and other phospholipids, as well as non-phosphorylated lipids such as cholesterol and triglycerides (14). The protein component consists of serum proteins, and surfactant proteins that were originally collectively thought to be specific to the lung or surfactant. However, this is no longer the case. Surfactant proteins, and especially the hydrophilic proteins (SP-A and SP-D) have been found in several other tissues (16–27).

Surfactant proteins (SP-A, SP-B, SP-C, and SP-D) are divided into two groups, by their hydrophobicity properties. The hydrophobic, surfactant protein B (SP-B), and C (SP-C) are primarily involved in the prevention of alveolar collapse at low lung volumes by lowering surface tension. SP-C stabilizes surfactant at low lung volumes, and since it has the ability to bind LPS, a role in innate immunity has been proposed for SP-C (28, 29). SP-A and SP-D are hydrophilic proteins that belong to the C-type lectin family (collectins), and are primarily host defense proteins (30, 31). SP-A has been shown to play an important role in the structure of the extracellular form of surfactant, tubular myelin, and other surfactant-related functions (32–34), and SP-D has been shown to play an important role in surfactant homeostasis (31, 35–37).

Members of the collectin family are characterized by an N-terminal collagen-like domain and a C-terminal carbohydrate recognition domain (CRD) that allows binding to various types of macromolecules, including carbohydrates, phospholipids, and proteins, as well to a number of pathogens and allergens (30). SP-A and SP-D are found in large oligomeric structures that bind viruses, bacteria and fungi in a calcium-dependent, and carbohydrate-specific manner (2, 38, 39), and it has been proposed that the oligomerization pattern may affect binding (40). The mature SP-A, a 248 amino acid (aa) protein (35kDa), associates in a trimeric structural subunit (105kDa), and six of these trimers assemble in a hexameric (630kDa) oligomeric bouquet-like structure that contains a total of eighteen SP-A1 and SP-A2 monomers. Both hetero-oligomers (i.e. consisting of both SP-A1, and SP-A2 monomers (41)), and homo-oligomers (i.e. consisting of SP-A1 or SP-A2 monomers) are functional (33, 42–46). SP-D oligomers are 540kDa cruciform tetrameric structures, comprised by four subunits (130kDa) of three 43kDa (375 aa) SP-D monomers each (39).

2.2. SP-A and SP-D functions in innate immunity

SP-A and SP-D are important components of the innate immune system (30). These molecules combat infections caused by bacteria, viruses, fungi, and other pathogens by mechanisms that may involve, among others, binding, aggregation, agglutination, inhibition of their growth, and promotion of their phagocytosis by immune cells (2, 30, 40, 47–50). Interaction between SP-A and the phagocytic cells, such as alveolar macrophages has also

been demonstrated, and shown to promote phagocytosis (43, 51, 52). Studies of interactions between SP-A or SP-D and pathogens, and between collectins and immune cells have been previously reviewed (36, 39, 53–59).

A number of soluble and membrane receptors have been shown to interact with collectins. SP-A is known to interact with CD35 (CR1) (60), C1qR (CD93) (61), CD14 (62), CD91/calreticulin complex (63), signal inhibitory protein α (SIRPα) (64, 65), SP-R210 (66), glycoprotein 340 (gp-340) (67), Toll-like receptors TLR-2 (68) and TLR-4 (69), and others (51, 66–68, 70–72). Some SP-A receptors have been identified in alveolar type II cells, but not in alveolar macrophages cell surface, indicating their potential role in surfactant function (73, 74), whereas others are ubiquitous (CD91/calreticulin, (64)). Most of the receptor molecules that interact with SP-A have also been shown to bind SP-D (SIRPα, CD91/calreticulin, gp-340, TLR-2, TLR-4, and CD14), and promote phagocytosis, clearance of apoptotic cells, modulate cytokine production, and/or act as opsonins, stimulating alveolar macrophage migration (39, 63, 65, 75–78).

Collectins facilitate destruction of various bacteria, viruses, and fungi, by at least two different mechanisms that involve either direct interaction with the pathogen, and/or activation of the immune cells (2, 36, 79–81). Both SP-A and SP-D can stimulate chemotaxis and enhance phagocytosis of alveolar macrophages, an important cellular component of the first line of defense of the lung. The influence of collectins on the interactions of alveolar macrophages with pathogens varies depending on the microorganism (57, 82). There is evidence that human SP-A binds and enhances phagocytosis of *Klebsiella pneumoniae* (83–85), *Escherichia coli*, *Staphylococcus aureus* (45, 86), and *Pseudomonas aeruginosa* (43, 52) by alveolar macrophages. SP-D has been shown to bind LPS from *Klebsiella pneumoniae*, and other bacteria (2). Furthermore, SP-A has also been found to promote macrophage production of pro- and anti-inflammatory cytokines (87).

SP-A and SP-D not only regulate the function of innate immune cells, but also interact and modulate the functions of dendritic cells, and other antigen-presenting cells, as well as T cells, providing a link between the innate and adaptative immune systems, in order to alleviate infection and inflammation in an attempt to restore tissue homeostasis (88).

2.3. Genetics of surfactant proteins

The two hydrophobic surfactant proteins, SP-B and SP-C, are encoded by a single gene, located in chromosomes 2 and 8, respectively. Their genetic complexities and polymorphisms associations with disease have been studied and reviewed elsewhere (12, 15, 89–94). The focus here is on SP-A and SP-D associations with disease, and therefore the hydrophobic surfactant proteins will not be discussed any further.

Human SP-A and SP-D are encoded by three genes (*SFTPA1*: SP-A1, *SFTPA2*: SP-A2, and *SFTPD*: SP-D), that have been mapped to chromosome 10q21–q23 (95–97). The human SP-A locus consists of two functional, highly homologous genes (SP-A1, and SP-A2) in opposite transcriptional orientation and a pseudogene being located between the two genes. These are found in a cluster along with the SP-D gene (Figure 1). The genetic complexity of SP-A1, SP-A2, and SP-D genes has been extensively studied, and reviewed (12, 98–103). SP-A1, SP-A2, and SP-D have all been found to be polymorphic (103–105). A particular locus is considered to be polymorphic if the less frequent allele has a population frequency of no less than 1%, and a heterozygosity frequency of at least 2%. Single nucleotide polymorphisms occur when a single nucleotide (purine or pyrimidine) in a DNA sequence is substituted with a different nucleotide. A SNP may either result in a synonymous or non-synonymous aa substitution, where the aa coded for is the same or different, respectively. The probability of recombination occurring within a haplotype partially depends on the

physical distance between the SNP loci. Closely spaced loci are therefore less likely to be separated and are described as being in linkage disequilibrium. Consequently, if the genotype of one SNP is known, the genotype of another SNP may be predicted if there is a high level of linkage disequilibrium between the two SNPs.

SP-A1 and SP-A2 genes are in linkage disequilibrium, and exhibit a similar genomic organization. The structure of both genes consists of four coding exons (I-IV) that show coding nucleotide differences that result in aa changes within the collagen-like domain of the protein, and these can distinguish between SP-A1 and SP-A2 gene products, and between their corresponding variants. Multiple SNPs have been identified in SP-A1 and SP-A2 coding regions, and UTRs (103, 106, 107). Nucleotide/aa changes at the coding region that determine the identity of SP-A1 and SP-A2 are shown in Table 1. In brief, both SP-A1 and SP-A2 protein molecules consist of 248 aa, and differ at the following residues: Met66, Asp73, Ile81, and Cys85 for SP-A1, and Thr66, Asn73, Val81, and Arg85 for SP-A2 (44, 102, 103, 108) (Table 1).

Several coding variants have been identified and characterized for each gene (98, 100, 102, 103, 108). These are combinations of several SNPs, and are summarized in Table 2. Variants 6A, $6A^2$, $6A^3$, and $6A^4$ are combinations of five biallelic SNPs within the exons of SP-A1, corresponding to aa positions 19, 50, 62, 133, and 219, and determined by combinations of SNPs rs1059047, rs1136450, rs1136451, rs1059057, and rs4253527, respectively. Two of these SNPs are silent (aa62 and aa133), whereas the remainder result in non-conservative aa substitutions. Similarly, SP-A2 variants 1A, $1A^0$, $1A^1$, $1A^2$, $1A^3$, and $1A^5$ involve four exonic SNPs at aa9, aa91, aa140, and aa223 (rs1059046, rs17886395, rs1965707, rs1965708, respectively), most of which result in a non-synonymous aa change, except for aa140, where a synonymous change occurs (103) (Table 2). These nine variants have been found in the population with different frequencies (103,104). The expression of SP-A1 and SP-A2 appears to differ among individuals as a function of age and lung health status (e.g. healthy vs. cystic fibrosis, culture positive vs. culture negative), as assessed by differences in the protein ratio of SP-A1 to total SP-A in human BAL samples (109).

In addition, splice and sequence differences are also found at the 5′ and 3′ untranslated regions (UTRs) of SP-A1 and SP-A2 genes (107, 108, 110, 111). At the 5′UTR, several exons (A, B, B′, C, C′, D, D′) splice in different configurations to give rise to a number of different 5′UTR variants for SP-A1 and SP-A2 (108). These have been shown to differentially impact SP-A regulation of gene expression (112, 113). Similarly, SNPs and other sequence variations located at the 3′UTR of SP-A1 and SP-A2 variants have also been shown to play a role in SP-A regulation (114).

The SP-D gene contains a total of eight exons, seven of which are coding. Exon I, and part of exon II correspond to the 5′UTR, and the last part of exon 8 corresponds to the 3′UTR. Coding and non-coding SNPs (rs721917, rs6413520, rs2243639, rs3088308, rs1051246, rs1923537, rs2245121, rs911887, rs2255601, and rs7078012) are also found within the SP-D gene (Table 3); most of these have been associated with a number of diseases (115–117). In addition, evidence indicates that serum SP-D levels are genetically influenced (106, 118–120).

Overall, the literature indicates that associations exist between SP-A or SP-D genetic variants that may include single nucleotide polymorphisms and haplotypes and the development of both chronic and acute lung diseases, as well as some non-pulmonary diseases. In the following paragraphs we discuss the clinical evidence of these associations.

3. ASSOCIATION OF SP-A AND SP-D POLYMORPHISMS WITH DISEASE

Variants of SP-A1, SP-A2, and SP-D genes have been found to associate with a range of pulmonary and non pulmonary diseases. A summary of the available information that significantly associated gene variants, SNPs and haplotypes of SP-A1, SP-A2, and SP-D with adult and pediatric disease is described below, and summarized in Table 4.

3.1. Respiratory pediatric and adult disease associations with SP-A1, SP-A2, and SP-D variants, SNPs and intragenic haplotypes

Since the lung is one of the major sites of surfactant protein synthesis, and because most surfactant proteins are involved collectively in surfactant-related functions, host defense, and regulation of inflammatory processes in the lung, it is expected that collectins play a role in clinical situations where surfactant homeostasis, and/or host defense mechanisms are affected. Therefore, it is not surprising that SP-A, and SP-D (as well as the hydrophobic surfactant proteins, which are not discussed in this review) are involved in the development of, or protection from, various pulmonary diseases (Table 4). In this section, we discuss SP-A and SP-D polymorphisms associations with adult and pediatric respiratory disease, and discuss potential interactions of collectins with viral, bacterial, fungal, and other disease-causing pathogens and molecules, as well as with the immune cells involved in pathogen clearance, and control of infection. It is likely that mechanisms involving function and regulation of collectins in human disease may overlap or differ entirely, depending on the physiologic context or derangement associated with each particular disease.

Different effects of SP-A and SP-D interactions with the same and/or different pathogens do occur. SP-A has been shown to enhance binding of alveolar macrophages to *Mycobacterium tuberculosis* (121), whereas SP-D binds to the bacterial surface causing a reduction in its uptake by alveolar macrophages (122). Interestingly, several SP-A and SP-D polymorphisms have been found to associate with risk for tuberculosis (117, 123–125). These include variants SP-A1 $6A^4$ (117), and SP-A2 $1A^3$ (117, 123) and $1A^5$ (123). Also, SP-A1 SNPs rs1136451 and rs4253527 (123), SP-A2 rs17886395 and rs1965708 (123), and SP-D rs721917 (117) and G459A (124) variation have been associated with TB.

Allergic diseases such as asthma and allergic rhinitis (AR) are very common multifactorial diseases, and polymorphisms in SP-A and SP-D genes have been associated with these diseases in several populations in three different clinical studies (126–130). Innate immunity collectins play a critical role in preventing damage and injury to nasal mucosa, which is constantly exposed to inhaled pollutants, microbes, and allergens. SP-A2 rs1965708 SNP was associated with increased risk for AR in a Chinese population (124). In addition, the SP-A2 $1A^2$ variant was found to be protective for AR (128), and the SP-A1 6A variant, and the 6A/1A haplotype were shown to associate with risk for asthma (129). For SP-D, a Threonine at aa11 (rs721917) was associated with increased risk for AR in the Chinese population (125). In contrast, a Methionine at aa11 (rs721917) was found to associate with risk for asthma in a black population (127). A study performed in a German population did not find any association of this SNP and susceptibility to asthma (123). The SP-D Met11Thr variant has been found to associate with assembly, function, and concentration of SP-D, with the Thr variant having a negative impact on these (131).

A small study conducted in an Indian population with allergic bronchopulmonary aspergillosis (ABPA), detected an association of the SP-A1 rs1136454, the SP-A2 rs1136452 SNPs (located at the collagen-like region), and an intronic SNP (rs1650223), with disease susceptibility, and severity of clinical markers of ABPA (total IgE levels and eosinophilia) (132). ABPA is caused by the pathogenic fungus *Aspergillus fumigatus*, and SP-A binds to various glycosylated allergens-antigens and glycoproteins from the fungus. In

addition, SP-A inhibits the *Aspergillus fumigatus*-induced histamine release from sensitized basophils (133), and enhances macrophage- and neutrophil-mediated clearance of the pathogen (133). Another small association study in an Indian population found the SP-A1 rs1059047, and SP-A2 rs17880902, rs17096771, and rs1965708 SNPs as risk determinants of high altitude pulmonary edema (HAPE), a disease characterized by increased capillary permeability due to exaggerated inflammation, and free radical-mediated lung injury (134). Together, these data indicate that SP-A polymorphisms may play a role in allergy control.

Chronic obstructive pulmonary disease (COPD) is characterized by chronic bronchitis, and/or emphysema. Elevated serum levels of SP-D are a biomarker for COPD (115), and a recent study associated the SP-D SNPs rs2245121, rs911887, rs6413520, rs721917, rs7078012, as well as the combination of rs1051246, rs2245121, rs911887, rs225601, rs6413520, and rs721917, with risk to develop COPD, and with SP-D serum levels, in independent populations, and multiple study designs (115). The authors proposed that the SP-D genetic variants may differentially modulate mechanisms involved in inflammatory signaling functions (135) and SP-D-mediated clearance of apoptotic cells (63), and that these may underline COPD pathogenesis (136, 137). Moreover, SP-A has been found to bind and enhance alveolar macrophage IFN-γ-mediated phagocytosis of *Mycoplasma pulmonis*, a pathogen involved in pneumonia and exacerbation of asthma, and COPD (138).

A significant association between SP-A1 $6A^3$, SP-A2 $1A^1$, or the combined haplotype $6A^3/1A^1$ with poor pulmonary outcomes in cystic fibrosis (CF) patients has been reported (139). Cystic fibrosis is an autosomal-recessive disease characterized by multi-organ disorders and decreased life expectancy, and recurrent or chronic airway infections with bacteria, including *Haemophilus influenzae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (140) Of relevance, differences in the phagocytic index of alveolar macrophages between SP-A1 and SP-A2 variants have been observed with regards to *Pseudomonas aeruginosa* and *Staphylococcus aureus* (43–45, 52). Moreover, pulmonary function deterioration is listed as one of the primary complications of CF, and surfactant proteins have been identified as candidates to mediate pathogenesis of pulmonary disease in CF (141). Decreased levels of SP-A and SP-D were detected in BAL from CF patients (141, 142) and attributed to persistent inflammation, which in turn increases degradation of collectins, and may also affect collectin synthesis (140). Of relevance, the SP-A2 $1A^1$ variant has the lowest activity for enhancement of TNF-α in THP-1 cells. Furthermore, both activities (phagocytosis and cytokine production) are negatively affected by oxidative stress (42, 45), a situation that may exist in the CF microenvironment, and may explain the compromised pulmonary innate immunity commonly seen in CF cases.

The SP-A1, $6A^4$ variant, and three SNPs: rs1136450, rs1136451, and rs4253527 were associated with risk to develop idiopatic pulmonary fibrosis (IPF) in a nonsmoker Mexican population (143). Derangement in pulmonary surfactant or its individual components and alveolar collapse are common findings in IPF, a progressive lung disorder characterized by sequential acute lung microinjuries, and fibroblastic foci formation, scarring, and end-stage, usually lethal, lung disease (144). The $6A^4$ variant exhibited differences in self-aggregation when compared with other SP-A variants that differ at aa219, in the CRD region (143). The authors proposed a Tryptophan at aa219 instead of Arginine (rs4253527) to be responsible for biochemical differences between $6A^4$ and other SP-A variants, and that these differences may affect SP-A1 ability to maintain the function, stability, and structure of surfactant.

Common SP-A1 ($6A^4$), and rare SP-A1 and SP-A2 ($6A^{11}$, $1A^9$) variants have been associated with risk for various types of lung cancer (145), when compared to normal and clinical controls. This study concluded that SP-A gene variants may be involved in mechanisms that influence susceptibility to lung cancer of a particular histological type.

These mechanisms may include modulation of inflammatory processes and host defense, defense against toxic gases, cigarette smoke, and other environmental factors, NF-kB activity (146, 147), modulation of cytokine production (42, 148, 149), and other determinants of cancer pathogenesis.

Polymorphisms in SP-A and SP-D genes have been linked to susceptibility to infection with respiratory syncytial virus (RSV) (150–153). RSV infection is the most common cause of hospitalization in infants, and the major cause of bronchiolitis during early childhood (154, 155). The risk of RSV infection was associated with the SP-A2 $1A^3$ variant, the $1A^1/1A^1$, and $1A^1/1A^3$ genotypes, and with the $6A^2/1A^3$ haplotype in a Finnish population (151). Asparagine at aa9 (rs1059046), Lysine at aa223 (rs1965708) of SP-A2 (151), as well as the SP-D SNP rs721917 (150) were also associated with risk. In contrast, Alanine at SP-A1 aa9 (rs1059047), and Proline at SP-A2 aa91 (rs17886395), were found to be protective (151). Other protective associations included the SP-A1 6A variant (151), SP-A2 variants $1A^2$ (152, 153), and 1A (151), $1A^0/1A^0$ genotype (153), and haplotypes, SP-A1/SP-A2 $6A^2/1A^3$ (151), SP-D Met11 (rs721917)/Ala160 (rs2243639) (152), and SP-A1/SP-A2/SP-D $6A^2/1A^0$/Ala160 (rs2243639) (152). SP-A has the ability to bind RSV virion glycoproteins and enhance its uptake by immune cells (156, 157). SP-D has also been found to bind the RSV fusion glycoprotein and decrease RSV infectivity (158).

3.2. Non-respiratory pediatric and adult disease associations with SP-A1, SP-A2, and SP-D variants, SNPs and intragenic haplotypes

The literature provides evidence of associations between SNPs and haplotypes of SP-A and SP-D genes with a number of non-respiratory diseases, either caused by diverse microorganisms, or in which the inflammatory/immune response is altered. In this section, we describe associations of polymorphisms in the collectins genes with diseases that occur outside the respiratory tract.

A study performed in an English population found that an SP-A2-specific, non synonymous SNP, rs1965708, was associated with susceptibility to infection, and increased risk of death by meningococcal disease (159). This sickness is caused by a bloodstream infection of *Neisseria meningitides* after a period of nasopharyngeal colonization (160). The risk allele exhibits a Lysine residue at aa223, located at the SP-A2 domain. Although, SP-A and SP-D are expressed at the site of initial meningococcal colonization, there is no evidence of SP-A binding to meningococci. The authors proposed other factors contributing to disease susceptibility, such as the ability of SP-A2 to bind SIRPα (64), altered inflammatory response, or inefficient handling of prior upper respiratory infections, which is known to affect susceptibility to meningococcal infection (161). The SP-A2 $1A^1$ variant that also contains Lysine at aa223 was associated with disease susceptibility, and the $1A^5$ variant that contains a Glutamine at the 223 residue was found to be protective. The $1A^1$ protein has a lower ability to stimulate TNF-α release when compared to 1A, $1A^0$, and $1A^2$ (148). The authors proposed a role of the lower TNF-α responses in the increased risk of death (162). Other common and rare SP-A2 variants ($1A^3$, $1A^8$) encode Lysine at aa223, but these occurred at low frequency in this and other studies.

Two independent groups analyzed associations of SP-A polymorphisms with susceptibility to otitis media, one of the most common infections of early childhood (163, 164), caused by bacterial pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* (165), and *Staphylococcus aureus*), or secondary to respiratory syncitial virus (RSV) infection (166). SP-A and SP-D are expressed in the Eustachian tube, and alterations in the expression or regulation of these molecules may also be the major risk factor for otitis media (167). The Finnish group identified the SP-A1/SP-A2 haplotypes $6A^2/1A^0$ as risk for acute, and $6A^4/1A^5$ as risk for acute and recurrent infection, and the SP-A1 $6A^2/6A^2$

genotype for recurrent otitis. Since SP-A binds to, and increases phagocytosis of *Streptococcus pneumoniae* and *Haemophilus influenzae,* the most common pathogens in acute otitis media (168), the authors proposed a distinct role of SP-A variants/haplotypes in disease pathogenesis (164). This study took place in Finland, and the distribution of SP-A haplotypes in this population has been shown to differ from frequencies found within the United States (169). This, along with potential differences in patient stratification, is probably one of the reasons why their results differ from those obtained by the American group, whose study population were infants at risk for asthma (163), with no distinction between acute and recurrent otitis media. In this study, the $6A^4$ variant, and the $6A^4/1A^5$ haplotype were protective for otitis media in white infants. SNP rs1059047, which is located within the N-terminal domain, was also associated with otitis media risk in infants with an Alanine at aa19, whereas infants with a valine at codon 19 were more likely to have otitis media during their first year of life. To date, the role of this SP-A1 domain in infection is unknown.

Recently, the SP-A1 rs1059047 (Alanine at aa19), and the SP-A2 rs1965708 (Glutamine at aa223) SNPs were found to associate with susceptibility to recurrent urinary tract infection (rUTI) (170), a disease caused by *Escherichia coli* and other microorganisms (171). Host genetic factors have been proposed to play an important role in the pathogenesis of rUTI, and polymorphisms within TLR-2 and TLR-4 genes were also identified to associate with rUTI (172). In addition, lower serum SP-A and SP-D levels correlated with these haplotypes and rUTI, and it is possible that different SP-A haplotypes result in variable SPA levels (99), and contribute to disease susceptibility.

In a recent study, two SP-D SNPs (rs2243639, and rs911887) were associated with ulcerative colitis (UC), a chronic inflammation of the colon, in a Japanese population. Like Crohn's disease, UC is caused by abnormal activation of the immune system in the intestines. Authors hypothesize that SP-D, by affecting dendritic cell and T-helper cell functions (70), modulates the inflammatory response. The SP-D association with UC is likely related to SP-D involvement the regulation of innate and adaptive immunity against bacteria in the colon (173). A study performed in a Norwegian population, subjects homozygous for the allele encoding Threonine at aa11 of SP-D (SNP rs721917) were found to exhibit higher risk for coronary artery stenosis, a type of cardiovascular disease, in which inflammation has been shown to play an important role (174). The C/C genotype (Thr/Thr) has been shown to correlate with lower serum SP-D levels, smaller oligomeric structures, lower affinity to pathogens, and susceptibility to lung disease (131). However, although it is known that SP-D plays an important role in lipid homeostasis, and removal of dying host cells, the authors conclude that SP-D variants are weakly associated with the atherogenic process. Interestingly, a polymorphism in the TLR-4 gene was also associated with coronary disease in this study; SP-D has been shown to bind TLR-4 via the CRD (175).

3.3. Newborn lung disease associations with SP-A1, SP-A2, and SP-D variants (SNPs and haplotypes)

Genetic associations with newborn disease, as well as their relationship with other factors (e.g. prematurity, use of pre-and post- partum treatment, such as antenatal corticoids, or mechanical ventilation, etc.) are of special interest, because of the potential that these associations hold to predict susceptibilities, and to help on decisions about the use of appropriate treatment. In this section, we focus on studies of SP-A and SP-D gene polymorphisms, and their association with two neonatal diseases, respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) that reflect, respectively, acute and chronic lung injury. A comparison of the main findings obtained in 13 different studies (11 for RDS, 2 for BPD), is shown in Table 5.

Deficiency of surfactant can result in RDS in prematurely born infants. Insufficient amounts of surfactant proteins, particularly SP-A, as well as absence of tubular myelin, an extracellular structural form of surfactant, have been shown to occur in RDS (176–180). Numerous studies have explored the relationship among SP-A1 and SP-A2 gene variants, and expression of SP-A in *in vitro* and *in vivo* models (32, 110, 114, 181, 182), however no clinical correlations among SP-A1, and/or SP-A2 haplotypes or variants, and SP-A levels in the lung have yet been fully described to date (109, 183). A specific SP-A1/SP-A2 haplotype, $6A^2/1A^0$, associated with RDS risk in most studies (184–186). In a particular study, this haplotype was only found to be a risk factor if twins were concordant for RDS (187). Another study identified an interaction of this haplotype with an SP-B polymorphism (Ile131Thr) (188), and the same interaction was found for $6A^3/1A^2$ and SP-B in protection (188).

The SP-A1 $6A^2$ variant has been associated with risk in the majority of the studies (184, 186, 189–191). These associations may be also dependent on SP-B polymorphisms (188, 192, 193), and influenced by multiple birth and birth order (187, 190), antenatal glucocorticoid therapy (11, 194, 195), size of the uterus and length of gestation (2). The SP-A1 $6A^2/6A^2$ genotype association with RDS susceptibility was also found to be influenced by multiple birth, being associated with risk when twins were concordant for RDS, or protective when twins were discordant for RDS (187, 190).

Variants $6A^3$ of SP-A1 (184, 185, 188, 192), and $1A^0$ of SP-A2 (184, 186, 192, 196) and other less frequent SP-A1 ($6A^4$) and SP-A2 ($1A^5$) variants (186) were associated with protection for RDS in several studies. In a separate study, the haplotype $6A^4/1A^5$ was found to be protective (186).

For SP-D, a non-coding SNP (rs1923537) was protective for RDS in a German study (116), and a different study identified several haplotypes of SP-A1, SP-A2, and SP-D that also associate with protection. These include haplotypes SP-A2/SP-D: $1A^1$-Thr160 (rs2243639), $1A^1$-Met11 (rs721917)-Thr160 (rs2243639), and SP-A1/SP-A2/SP-D: $6A^4$-$1A^2$-Tr160 (rs2243639), $6A^3$-$1A^1$-Met11 (rs721917)-Thr160 (rs2243639), and $6A^4$-$1A^2$-Met11 (rs721917)-Thr160 (rs2243639) (197).

BPD is the most common chronic lung disease in infants. A number of antenatal and postnatal risk factors influence susceptibility to BPD. SP-A2/SP-D haplotypes were found to protect against BPD: 1A2-Ala160 (rs2243639), and 1A2-Thr11 (rs721917)-Ala160 (rs2243639) (198), and an association between the rare SP-A1 $6A^6$ variant and risk for BPD has also been reported (199).

3.4. SP-A, and SP-D polymorphisms found in more than one study group

Several SP-A1, and SP-A2 genetic variants, as well as, specific SP-A1, SP-A2, and SP-D SNPs were found to associate with lung disease susceptibility in more than one study group. A previous review has described these associations (12). We provide an updated summary of this information, and also included associations with non-respiratory diseases in Tables 6 (SNPs) and Table 7 (gene variants).

4. ASSOCIATION OF SP-A AND SP-D SERUM AND BRONCHOALVEOLAR LAVAGE FLUID (BAL) PROTEIN LEVELS WITH DISEASE

Collectins are considered to be markers of and/or contributors to the pathogenesis of various diseases characterized by inflammation, infection, and/or derangement of pulmonary function or integrity. Although associations of SP-A and SP-D gene polymorphisms and disease have been observed, to date, no human disease has been identified to be the result of

one or more SPA or SP-D gene polymorphisms. However, clinical conditions have been identified where a) the amounts of SP-A, SP-D, as well as the SP-A1/SP-A ratio in BAL or serum are altered, and b) host defense and inflammation mechanisms mediated by collectins are deranged. Association studies have correlated clinical outcomes and collectins concentrations (140–142, 200–251). These associations may underline the contribution SP-A and SP-D make to innate host defense by altering cytokine production, enhancing immune cells chemotaxis and function, and regulating cell proliferation and apoptosis, as well as the previously decribed interaction with pathogens (252, 253). In Table 8 we have reviewed and summarized the clinical studies that correlated significant changes in serum and BAL SP-A and SP-D protein levels with pulmonary and non-pulmonary disorders. We present the information as increases/decreases compared to control subjects for each study. The absolute SP-A and SP-D levels are not reported due to potential variation among studies that may arise from the use of different antibodies and standards.

The literature provides evidence that SP-A and SP-D levels are influenced by age, health, and smoking status, circadian rhythm, as well as by genetic factors (106, 109, 118, 120, 232, 254–257). However, very few studies have correlated genetic polymorphisms with collectins serum levels. In one study, an SP-D haplotype revealed a negative association with serum SP-D levels (118). In addition, the SP-D rs721917 SNP has been shown to influence oligomerization, function, and serum concentration of SP-D (131). With regards to SP-A, since the functional activity of SP-A1 and SP-A2 has been shown to differ (33, 43, 44, 52), the overall functional activity of human SP-A cannot be assessed if total SP-A levels are reported. Therefore, the relative SP-A1/SP-A2 ratio is likely to be more informative of the total functional SP-A activity in the lung, and potentially provide a more disease-specific marker, especially if it is further correlated with the specific SP-A1 and SP-A2 genotype. Future studies may focus on potential correlations among SP-A and SP-D genetic polymorphisms, protein levels, and susceptibility to disease, and provide further evidence of collectins as genetic biomarkers for disease.

5. SUMMARY

We have reviewed the available experimental evidence of SP-A1, SP-A2, and SP-D genetic associations with disease susceptibility in adults, children, and newborns. Interactions among these and other genes products, as well as the impact of environmental factors, and other genetic and non-genetic factors are a necessary extension of this work, and will broaden our knowledge about the complexities underlying the role of collectins in respiratory disease. Understanding these complexities, and the impact of genetic variability will help us understand individual disease-susceptibilities, identify risk groups, permit early detection of risk in neonates, and therefore design proper interventions in an attempt to decrease the long-term pulmonary injury.

Acknowledgments

This work was supported by the NIH HL-34788 grant.

Abbreviations

SNP	single nucleotide polymorphism
SFTPA	SP-A, surfactant protein A
SFTPD	SP-D, surfactant protein D
TNF-α	tumor necrosis factor alpha

IFNγ	interferon gamma
CRD	carbohydrate recognition domain
aa	amino acid
LPS	lipopolisaccharide

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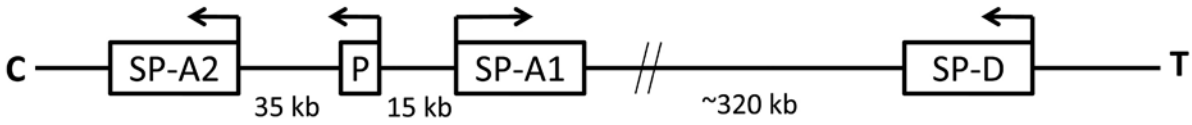

A

B

Gene	Database	Gene name / gene id	Strand	Start position	End position
SP-A2	GenBank	SFTPA2 - 729238	negative	81320163	81315608
	Ensembl	ENSG00000185303	negative	81320163	81315608
P	GenBank	SFTPA3P - 100288405	negative	81355491	81355045
	Ensembl	ENSG00000225827	negative	81355416	81355050
SP-A1	GenBank	SFTPA1 - 653509	positive	81370695	81375199
	Ensembl	NSG00000122852	positive	81370701	81375202
SP-D	GenBank	SFTPD - 6441	negative	81708861	81697496
	Ensembl	ENSG00000133661	negative	81742370	81697496

Figure 1. SP-A and SP-D loci on chromosome 10

Diagrammatic representation of the 10q22–23 region of the human chromosome 10 (not to scale). The human surfactant protein A locus consists of two functional genes (SP-A1, SP-A2) located in opposite transcriptional orientation, and a pseudogene (P). The SP-D locus is located closer to the telomere (T) in the negative strand, as are SP-A2 and P (Panel A). The information with regards to the specific locations of these genetic loci, available at the GenBank (www.ncbi.nlm.nih.gov/genbank/) and Ensembl (www.ensembl.org/) databases is shown in Panel B. Positive strand refers to the DNA orientation (5′-3′) from C to T, whereas negative strand refers to the opposite orientation.

Table 1

Amino acid differences that distinguish between human SP-A1 and SP-A2

	Amino acid position[1]			
	66	**73**	**81**	**85**
SP-A1	ATG (Met)	GAT (Asp)	ATC (Ile)	TGT (Cys)
SP-A2	ACA (Thr)	AAT (Asn)	GTC (Val)	CGT (Arg)

[1] Numbering of amino acid position is based on the precursor molecule that includes the signal peptide

Table 2

SNP and/or amino acid variation within the coding region of SP-A1 and SP-A2, that distinguish among the most frequently observed SP-A1 and SP-A2 variants or intragenic haplotypes

			SP-A1 variants					
SNP id	**Nucleotide**	**amino acid substitution**[a]	**6A**	**6A^2**	**6A^3**	**6A^4**		
rs1059047	T/C	aa19: GTG (Val) > GCG (Ala)	C (Ala)	T (Val)	T (Val)	T (Val)		
rs1136450	C/G	aa50: CTC (Leu) > GTC (Val)	C (Leu)	G (Val)	C (Leu)	C (Leu)		
rs1136451	A/G	aa62: CCA (Pro) > CCG (Pro)	G (Pro)	A (Pro)	A (Pro)	G (Pro)		
rs1059057[b]	A/G	aa133: ACA (Trp) > ACG (Trp)	G (Trp)	A (Trp)	A (Trp)	A (Trp)		
rs4253527	C/T	aa219: CGG (Arg) > TGG (Trp)	C (Arg)	C (Arg)	C (Arg)	T (Trp)		
			SP-A2 variants					
SNP id	Nucleotide	amino acid substitution[a]	1A	1A^0	1A^1	1A^2	1A^3	1A^5
rs1059046	A/C	aa9: ACC (Thr) > AAC (Asn)	C (Thr)	A (Asn)	C (Thr)	C (Thr)	A (Asn)	C (Thr)
rs17886395	G/C	aa91: GCT (Ala) > CCT (Pro)	C (Pro)	G (Ala)	G (Ala)	G (Ala)	G (Ala)	C (Pro)
rs1965707[b]	C/T	aa140: TCC (Ser) > TCT (Ser)	C (Ser)	C (Ser)	T (Ser)	C (Ser)	T (Ser)	T (Ser)
rs1965708	C/A	aa223: CAG (Gln) > AAG (Lys)	C (Gln)	C (Gln)	A (Lys)	C (Gln)	A (Lys)	C (Gln)

[a]Numbering of amino acid (aa) position is based on the precursor molecule that includes the signal peptide,

[b]These SNPs have been identified in SP-D but have not been associated with any disease described in the present review.

Table 3

Human SP-D SNPs

SNP id	Nucleotide	amino acid substitution[1]
rs721917	C/T	aa11: A**T**G (Met) > A**C**G (Thr)
rs6413520	T/C	aa25: AG**T** (Ser) > AG**C** (Ser)
rs2243639	A/G	aa160: **A**CA (Thr) > **G**CA (Ala)
rs3088308[2]	A/T	aa270: **T**CT (Ser) > **A**CT (Thr)
rs1051246[2]	C/T	aa286: GC**T** (Ala) > GC**C** (Ala)
rs1923537	T/C	**3′UTR**
rs2245121	A/G	**intron**
rs911887	A/G	**Intron**
rs2255601[2]	G/A	**Intron**
rs7078012	C/T	**Intron**

[1] Numbering of amino acid (aa) position is based on the mature protein and does not include signal peptide,

[2] These SNPs have been identified in SP-D but have not been shown to associate with any disease at present.

Table 4

SP-A and SP-D SNP associations with adult and pediatric disease

Disease studied	Gene(s)	Population	SNP or haplotype	nucleotide (amino acid)	susceptibility	cases	controls	Reference
ABPA	SP-A1	Indian	rs1136454 (G/A)	G (Arg)	risk	22	23	(132)
ABPA	SP-A1/SP-A2	Indian	rs1136454-rs1136452 (C/G)	G(Arg)-G(Ala)	risk	22	23	(132)
ABPA	SP-A2	Indian	rs1650223 (intron)		risk	10	11	(132)
AR	SP-A2	Chinese	rs1965708	A (Lys)	risk	216	84	(128)
AR	SP-A2	Chinese	$1A^2$		protective	216	84	(128)
AR	SP-D	Chinese	rs721917	C (Thr)	risk	216	84	(127)
Asthma	SP-A1	mixed	6A		risk	221	355[a]	(129)
Asthma	SP-A1/SP-A2	mixed	6A/1A		risk	221	355[a]	(129)
Asthma	SP-D	German			no association	322	270	(126)
Asthma	SP-D	Black	rs721917	T (Met)	risk	162	97	(130)
Cardiovascular Disease (CS)	SP-D	Norwegian	rs721917	C/C (Thr/Thr)	risk	130	100	(174)
CF	SP-A1	Caucasian	$6A^3$		risk	135[b]	n/a	(139)
CF	SP-A2	Caucasian	$1A^1$		risk	135[b]	n/a	(139)
CF	SP-A1/SP-A2	Caucasian	$6A^3/1A^1$		risk	135[b]	n/a	(139)
COPD	SP-D	Caucasian	rs2245121	A	risk	389	472	(115)
COPD	SP-D	Caucasian	rs911887	G	risk	389	472	(115)
COPD	SP-D	Caucasian	rs6413520	C (Ser)	risk	389	472	(115)
COPD	SP-D	Caucasian	rs721917	C (Thr)	risk	389	472	(115)
COPD	SP-D	Caucasian	rs7078012	C	risk	389	472	(115)
COPD	SP-A1	Mexican	rs1136451	A (Pro)	risk	101	81	(258)
HAPE	SP-A1	Indian	rs1059047	C (Ala)	risk	27	19	(134)
HAPE	SP-A2	Indian	rs17880902 (T/C)	T (Asp)	risk	27	19	(134)
HAPE	SP-A2	Indian	rs17096771 (T/C)	T (Pro)	risk	27	19	(134)
HAPE	SP-A2	Indian	rs1965708	C (Gln)	risk	27	19	(134)
IPF	SP-A1	Mexican	$6A^4$		risk	84	194	(143)
IPF	SP-A1	Mexican	rs1136450	C (Leu)	risk	84	194	(143)

Disease studied	Gene(s)	Population	SNP or haplotype	nucleotide (amino acid)	susceptibility	cases	controls	Reference
IPF	SP-A1	Mexican	rs1136451	G (Val)	risk	84	194	(143)
IPF	SP-A1	Mexican	rs4253527	T (Trp)	risk	84	194	(143)
Lung Cancer (SCC)	SP-A1	German	$6A^4$		risk	35	110[c]	(145)
Lung Cancer (SCC)	SP-A1	German	$6A^4$		risk	35	99[d]	(145)
Lung Cancer (NSCLC)	SP-A1	German	$6A^{11}$		risk	68	110[c]	(145)
Lung Cancer (NSCLC)	SP-A2	German	$1A^9$		risk	68	110[c]	(145)
Lung Cancer (AC)	SP-A1	German	$6A^{11}$		risk	23	110[c]	(145)
Lung Cancer (AC)	SP-A2	German	$1A^9$		risk	23	99[d]	(145)
Meningococcal Disease	SP-A2	English	rs1965708	A (lys)	risk	303	222	(159)
Meningococcal Disease	SP-A2	English	$1A^1/1A^1$		risk	303	222	(159)
Meningococcal Disease	SP-A2	English	$1A^5$		protective	303	222	(159)
Otitis Media	SP-A1/SP-A2	Finnish	$6A^2/1A^0$		risk	47 (acute)	228	(164)
Otitis Media	SP-A1/SP-A2	Finnish	$6A^4/1A^5$		risk	47 (acute), 147 (recurrent)	228	(164)
Otitis Media	SP-A1	Finnish	$6A^2/6A^2$		risk	147 (recurrent)	228	(164)
Otitis Media	SP-A1	mixed	$6A^4$		protective	258	355[a]	(163)
Otitis Media	SP-A1/SP-A2	mixed	$6A^4/1A^5$		protective	258	355[a]	(163)
Otitis Media	SP-A1	mixed	rs1059047	C (Ala)	risk	258	355[a]	(163)
rUTI	SP-A1	Chinese	rs1059047	C (Ala)	risk	32	30	(170).
rUTI	SP-A2	Chinese	rs1965708	C (Gln)	risk	32	30	(170).
RSV	SP-A2	mixed	rs1059046	A (Asn)	risk	277	n/a	(153)
RSV	SP-A2	mixed	$1A^0/1A^0$		protective	277	n/a	(153)
RSV	SP-A2	mixed	$1A^2$		protective	277	n/a	(153)
RSV	SP-A2	mixed	$1A^2$		protective	148	n/a	(152)
RSV	SP-D	mixed	rs2243639	A (Thr)	risk (possible)	148	n/a	(152)
RSV	SP-D	mixed	rs721917-rs2243639	T(Met)-G(Ala)	protective	148	n/a	(152)
RSV	SP-A1/SP-A2/SP-D	mixed	$6A^2$-$1A^0$-rs2243639	G (Ala)	protective	148	n/a	(152)
RSV	SP-A2	Finnish	$1A^3$		risk	86	95	(151)

Disease studied	Gene(s)	Population	SNP or haplotype	nucleotide (amino acid)	susceptibility	cases	controls	Reference
RSV	SP-A2	Finnish	1A		protective	86	95	(151)
RSV	SP-A1	Finnish	6A		protective	86	95	(151)
RSV	SP-A1/SP-A2	Finnish	6A/1A		protective	86	95	(151)
RSV	SP-A1	Finnish	rs1059047	C (Ala)	protective	86	95	(151)
RSV	SP-A2	Finnish	rs17886395	C (Pro)	protective	86	95	(151)
RSV	SP-A2	Finnish	rs1965708	A (Lys)	risk	86	95	(151)
RSV	SP-A2	Finnish	$1A^1/1A^1$		risk	86	95	(151)
RSV	SP-A2	Finnish	$1A^0/1A^3$		risk	86	95	(151)
RSV	SP-A1/SP-A2	Finnish	$6A^2/1A^3$		risk	86	95	(151)
RSV	SP-D	Finnish	rs721917	T (Met)	risk	84	93	(150)
TB	SP-D	Indian	G459A (exon 7)[e]		risk	30	30	(124)
TB	SP-D	Mexican	rs721917	C (Thr)	risk	178	101	(117)
TB	SP-A1	Mexican	$6A^4$		risk	178	101	(117)
TB	SP-A2	Mexican	$1A^3$		risk	178	101	(117)
TB	SP-A2	Ethiopian	$1A^3$		risk	226 (181 families)	n/a	(123)
TB	SP-A2	Ethiopian	$1A^5$		risk	226 (181 families)	n/a	(123)
TB	SP-A1	Ethiopian	rs1136451	A (Pro)	risk	226 (181 families)	n/a	(123)
TB	SP-A1	Ethiopian	rs4253527	T (Trp)	risk	226 (181 families)	n/a	(123)
TB	SP-A2	Ethiopian	rs17886395	C (Pro)	risk	226 (181 families)	n/a	(123)
TB	SP-A2	Ethiopian	rs1965708	C (Gln)	risk	226 (181 families)	n/a	(123)
UC	SP-D	Japanese	rs911887	G	risk	296	394	(22)
UC	SP-D	Japanese	rs2243639-rs911887	A (Thr)-G	risk	296	394	(22)

ABPA: allergic bronchopulmonary aspergillosis; AR: allergic rhinitis; CS: coronary stenosis; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; HAPE: high altitude pulmonary edema; IPF: idiopathic pulmonary fibrosis; SCC: squamous cell carcinoma; NSCLC: non-small cell lung cancer; AC: adenocarcinoma; rUTI: recurrent urinary tract infection; RSV: respiratory syncytial virus infection; TB: tuberculosis; UC: ulcerative colitis.

[a] infants at risk,

[b] cases were stratified according to pulmonary outcomes (e.g. predicted FEV1, etc), and the risk variants were associated with cases of poor pulmonary outcome,

[c] healthy controls,

[d] clinical controls,

[e] SNP id not available.

Table 5

SP-A and SP-D SNP associations with neonatal disease

Disease studied	Gene(s)	Population	SNP or haplotype	nucleotide (amino acid)	susceptibility	cases	controls	Reference
BPD	SP-A1	German	$6A^6$		risk	23	23	(199)
BPD	SP-A2/SP-D	Greek	$1A^2$-rs2243639	G (Ala)	protective	71 (60 families)		(198)
BPD	SP-A/SP-D	Greek	$1A^2$-rs721917-rs2243639	C(Thr)-G(Ala)	protective	71 (60 families)		(198)
RDS	SP-A1	Chinese	$6A^2$		risk	18	28	(191)
RDS	SP-D	German	rs1923537 (3′UTR)	G/G	protective	202	68	(116)
RDS	SP-A2/SP-D	mixed	$1A^1$-rs2243639	A (Thr)	protective	132 families		(197)
RDS	SP-A2/SP-D	mixed	$1A^1$-rs721917-rs2243639	T(Met)-A(Thr)	protective	132 families		(197)
RDS	SP-A1/SP-A2/SP-D	mixed	$6A^4$-$1A^2$-rs2243639	A (Thr)	protective	132 families		(197)
RDS	SP-A1/SP-A2/SP-D	mixed	$6A^3$-$1A^1$-rs721917-rs2243639	T(Met)-A(Thr)	protective	132 families		(197)
RDS	SP-A1/SP-A2/SP-D	mixed	$6A^4$-$1A^2$-rs721917-rs2243639	T(Met)-A(Thr)	protective	132 families		(197)
RDS	SP-A1	Finnish	$6A^2$		protective[d]	198[a]		(187)
RDS	SP-A1	Finnish	$6A^2/6A^2$		protective[d]	198[a]		(187)
RDS	SP-A1/SP-A2	Finnish	$6A^2/1A^0$		protective[d]	198[a]		(187)
RDS	SP-A1	Finnish	$6A^2$		risk[b]	441/480[c]		(190)
RDS	SP-A1	Finnish	$6A^2/6A^2$		risk[b]	441/480[c]		(190)
RDS	SP-A1/SP-A2	Finnish	$6A^2/1A^0$		risk	86 (76 families)	35 (31 families)	(184)
RDS	SP-A1	Finnish	$6A^2$		risk	88 (76 families)	35 (31 families)	(184)
RDS	SP-A1	Finnish	$6A^3$		protective	88 (76 families)	35 (31 families)	(184)
RDS	SP-A2	Finnish	$1A^0$		risk	93 (76 families)	38 (31 families)	(184)
RDS	SP-A1	Finnish	$6A^2$		risk	46	43	(185)
RDS	SP-A1	Finnish	$6A^3$		protective	46	43	(185)
RDS	SP-A1/SP-A2	Finnish	$6A^2/1A^0$		risk	88	88	(185)
RDS	SP-A1	mixed	$6A^2$		risk	122 (32 families)		(186)
RDS	SP-A1	mixed	$6A^4$		protective	122 (32 families)		(186)
RDS	SP-A2	mixed	$1A^0$		risk	122 (32 families)		(186)

Disease studied	Gene(s)	Population	SNP or haplotype	nucleotide (amino acid)	susceptibility	cases	controls	Reference
RDS	SP-A2	Mixed	$1A^5$		protective	122 (32 families)		(186)
RDS	SP-A1/SP-A2	Mixed	$6A^2/1A^0$		risk	122 (32 families)		(186)
RDS	SP-A1/SP-A2	Mixed	$6A^4/1A^5$		protective	122 (32 families)		(186)
RDS	SP-A1	Finnish	$6A^2$		risk[e]	184	500	(188)
RDS	SP-A1	Finnish	$6A^3$		protective[e]	184	500	(188)
RDS	SP-A1/SPA2	Finnish	$6A^2/1A^0$		risk[e]	184	500	(188)
RDS	SP-A1/SP-A2	Finnish	$6A^3/1A^2$		protective[e]	184	500	(188)
RDS	SP-A1	Black	$6A^3$		protective[g]	40	38	(192)
RDS	SP-A1	Caucasian	$6A^2$		risk[f]	203	331	(192)
RDS	SP-A2	Caucasian	$1A^0$		risk[f]	203	331	(192)
RDS	SP-A2	Caucasian	$1A^0$		risk	106	86	(196)

RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia;

[a] twin pairs;

[b] singletons;

[c] twin or multiple infants;

[d] protective if twins are discordant for RDS, but risk if twins are concordant for RDS;

[e] together with SP-B Thr/Thr genotype at Ile131Thr polymorphism;

[f] together with the SP-B genotype 9306(A/G) or intron 4 (del/*);

[g] together with the SP-B genotype 1580(T/T).

Table 6

Summary of SP-A1, SP-A2, and SP-D SNPs and disease susceptibility

Gene	SNP	Nucleotide (aa)	Risk	Protection
SP-A1	rs1059047	C (Ala)	HAPE	RSV
			Otitis Media	
			rUTI	
	rs1136450	C (Leu)	IPF	
	rs1136451	A (Pro)	COPD	
			TB	
		G (Val)	IPF	
	rs4253527	T (Trp)	IPF	
			TB	
SP-A2	rs1059046	A (Asn)	RSV	
	rs17886395	C (Pro)	TB	RSV
	rs1965708	A (Lys)	AR	
			Meningococcal Disease	
			RSV	
		C (Gln)	HAPE	
			rUTI	
			TB	
SP-D	rs721917	C (Thr)	AR	BPD[1]
			Cardiovascular (CS)	RDS[1]
			COPD	
			TB	
		T (Met)	Asthma	RSV[2]
			RSV	
	rs6413520	C (Ser)	COPD	
	rs2243639	A (Thr)	RSV	RDS[1]
			UC	
		G (Ala)		RSV[1]
				BPD[1]
				RDS[3]
	rs1923537	G		RDS
	rs2245121	A	COPD	
	rs911887	G	COPD	
			UC	
	rs7078012	C	COPD	

AR: allergic rhinitis; BPD: bronchopulmonary dysplasia; CS: coronary stenosis; COPD: chronic obstructive pulmonary disease; HAPE: high altitude pulmonary edema; IPF: idiopathic pulmonary fibrosis; rUTI: recurrent urinary tract infection; RDS: respiratory distress syndrome; RSV: respiratory syncytial virus infection; TB: tuberculosis; UC: ulcerative colitis.

[1] haplotypes with SP-A1 and/or SP-A2 polymorphisms;

[2] haplotype with SP-D rs2243639;

[3] both SNP alleles were associated with protection, depending on the population

Table 7

Summary of SP-A1 and SP-A2 genetic variants and disease susceptibility

Gene	Variant	Risk	Protection
SP-A1	6A	Asthma	RSV
		CF	
	$6A^2$	Otitis Media	
		RSV[a]	
		RDS	
	$6A^3$	CF	RDS
	$6A^4$	IPF	Otitis Media[b]
		Lung cancer	RDS[b]
	$6A^6$	BPD	
	$6A^{11}$	Lung cancer	
SP-A2	1A	Asthma[a]	RSV
	$1A^0$	RDS	
		Otitis Media RSV[c]	
	$1A^1$	CF	RDS[a]
		RSV	
	$1A^2$		AR
			BPD[a]
			RDS[a]
			RSV
	$1A^3$	RSV	
		TB	
	$1A^5$	Otitis Media[a]	RDS
		TB	

AR: allergic rhinitis; BPD: bronchopulmonary dysplasia; CF: cystic fibrosis; IPF: idiopathic pulmonary fibrosis; RDS: respiratory distress syndrome; RSV: respiratory syncytial virus infection; TB: tuberculosis.

[a] only in haplotypes (with SP-A or SP-D),

[b] in Otitis Media, $6A^4$ is risk if in haplotype with $1A^5$, but in RDS remains protective if in haplotype with $1A^5$,

[c] risk in $1A^0/1A^3$, protectivein $1A^0/1A^0$.

Table 8

SP-A and SP-D protein levels in disease, and other clinical conditions, compared to control.

Disease	Serum levels		References	BAL levels		References
	SP-A	SP-D		SP-A	SP-D	
Asthma		↑	(200)	↓		(226)
				↑	↑	(227)
BPD				↓		(228)
Bronchitis	↑		(201)			
CF		↑	(202)	↓ (no infection)		(142)
					↓ (no infection)	(140, 141)
				↑ (infection)		(229)
					↓ (infection)	(140, 141)
CLE	↑		(203)			
COPD	↑		(204)	↑*1*		(230, 231)
		↑	(205)		↓	(232)
HP		↑	(206)	↑		(233, 234)
IPF	↑		(207–212)	↓		(235, 236)
		↑	(210, 211, 213, 214)			
Lung trauma				↓		(237)
Measles		↑	(215)			
PAP	↑		(207)	↑		(207, 238)
		↑	(210)	↑*2*		(239)
					↑	(210, 240, 241)
Pneumonia		↑	(213, 216, 217)	↓		(242–244)
				↑ (HIV +)		(244, 245)
					↑	(217)
RA		↓	(218, 219)			
RDS	↑		(203, 220–222)	↓		(242, 246, 247)
	↓		(223)		↓	(248, 249)

Disease	Serum levels		References	BAL levels		References
	SP-A	SP-D		SP-A	SP-D	
		↑	(211, 221, 224)	↓[2]	↓[2]	(249)
RSV					↓	(251)
Sarcoidosis		↑	(210, 225)	↑		(233)
					↑	(210)
TB		↑	(210)			

BPD: bronchopulmonary dysplasia, CF: cystic fibrosis, CLE: cardiac lung edema, HP: hypersensitivity pneumonitis, IPF: idiopatic pulmonary fibrosis, PAP: pulmonary alveolar proteinosis, RA: rheumatoid arthritis, RDS: respiratory distress syndrome, RSV: respiratory syncytial virus infection, TB: tuberculosis.

[1]Levels measured in induced sputum and lung tissue,

[2]The samples from these studies are from tracheal aspirates