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Inherited Surfactant Disorders

W. Adam Gower, MD,* Susan E. Wert, PhD,† Lawrence M. Nogee, MD‡

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Objectives  After completing this article, readers should be able to:

1. Recognize the clinical presentations resulting from inherited disorders of surfactant metabolism.
2. Describe the roles of surfactant protein (SP)-B, adenosine triphosphate–binding cassette member A3 (ABCA3), and SP-C in surfactant function and metabolism.
3. Evaluate infants for suspected inherited surfactant disorders and recognize the limitations of such studies.
4. Delineate how rare disorders can provide insights into normal metabolism and the pathogenesis of more common illnesses.

Abstract
Inherited disorders of surfactant metabolism are rare causes of respiratory disease in newborns but are associated with significant morbidity and mortality. This review outlines the molecular basis and pathophysiology of the three currently identified single-gene disorders of surfactant metabolism as well as the clinical presentations and evaluation of potentially affected infants. Implications for the understanding of normal surfactant metabolism and the potential roles of surfactant dysfunction mutations in more common neonatal disorders, such as respiratory distress syndrome, are also discussed.

Introduction
Pulmonary surfactant is the mixture of lipids and specific proteins that reduces surface tension at the air-liquid interface and prevents end-expiratory atelectasis. Lack of pulmonary surfactant due to decreased production from pulmonary immaturity is the principal cause of respiratory distress syndrome (RDS) in preterm infants. RDS is a relatively common disorder, affecting more than 50% of infants born at 30 weeks’ or less gestation, but modern methods of respiratory support and exogenous surfactant replacement therapy have aided in keeping mortality from RDS low. Surfactant deficiency also may result from genetic mechanisms that disrupt the production of key proteins important in surfactant function and metabolism. Although these single-gene disorders are rare, their associated morbidity and mortality are very high. Thus, recognition of these disorders is important to counsel families properly concerning prognosis, and because they are genetic in origin, recurrence risk. In addition, the study of these disorders has offered insight into normal aspects of surfactant metabolism and can provide clues to genes that may be important in influencing the risk for RDS in preterm infants. In this

Abbreviations
ABCA3: adenosine triphosphate–binding cassette member A3
DPPC: dipalmitoyl phosphatidylcholine
DSPC: disaturated phosphatidylcholine
ILD: interstitial lung disease
PC: phosphatidylcholine
PG: phosphatidylglycerol
RDS: respiratory distress syndrome
SP: surfactant protein
TTF-1: thyroid transcription factor-1

*Eudowood Division of Pediatric Respiratory Sciences, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md.
†Divisions of Neonatology and Pulmonary Biology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center & University of Cincinnati College of Medicine, Cincinnati, Ohio.
‡Eudowood Neonatal Pulmonary Division, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md.
article, we review the known inherited disorders of surfactant metabolism, focusing on their clinical features, diagnosis, and implications for lung biology.

**Surfactant Function, Components, and Metabolism**

Pulmonary surfactant is synthesized by alveolar type II cells of the lung and stored within lamellar bodies, which are lysosomally derived organelles specific to these cells. Structurally, lamellar bodies consist of well-organized concentric rings of lipid membrane surrounding an electron-dense core, as observed by electron microscopy. Surfactant is secreted by exocytosis after fusion of the lamellar body with the plasma membrane. Surfactant may be either recycled through type II cells or catabolized by alveolar macrophages. Phosphatidylcholine (PC) (also known as lecithin) is the principal phospholipid in surfactant needed for lowering of surface tension, in particular, dipalmitoyl PC (DPPC) or disaturated PC (DSPC), which accounts for approximately half of surfactant by weight. Precisely how surfactant becomes enriched for DSPC is not known.

Two low-molecular weight, extremely hydrophobic proteins, surfactant protein (SP) B and C, facilitate the adsorption of surfactant lipids to the air-liquid interface after secretion and are essential for surfactant’s surface tension-lowering properties. Both SP-B and SP-C are found in varying amounts in the mammalian-derived exogenous surfactants used to treat preterm babies who have RDS. Surfactant also contains two larger, more hydrophilic, structurally related glycoproteins, SP-A and SP-D. These proteins are involved primarily in innate immunity and immunomodulation, with more limited roles in surface tension-lowering and metabolism. (1) Genetic diseases related to abnormalities in SP-A and SP-D production have not yet been reported.

**Genetic Lung Disease Due to SP-B Deficiency**

SP-B is a 79-amino acid protein derived from a much larger precursor protein (proSP-B) encoded by a single gene (*SFTPB*) on chromosome 2. Proteolytic cleavage of amino- and carboxyterminal domains from proSP-B yields the mature form of SP-B found in the airspaces. The final processing steps are specific to type II cells and occur in lamellar bodies or their immediate precursors. (2)(3)

*SFTPB* contains ten coding exons, with mature SP-B encoded in exons 6 and 7. SP-B expression is regulated developmentally, increasing dramatically in late gestation. Sequences in the 5’ untranslated region critical for the developmental and cell-specific regulation of SP-B have been identified, as have transcription factors needed for its expression, most notably thyroid transcription factor 1 (TTF-1) (also known as Nkx2.1). (4) Many commonly occurring polymorphisms have been identified in the SP-B gene, including one in the promoter region that affects the level of SP-B gene transcription. (5) Another in exon 4 determines whether N-linked glycosylation occurs in the aminoterminal domain of the proprotein (6) and, thus, may be functionally significant. An extensively characterized variable nucleotide tandem repeat region in intron 4 may be associated with a risk for RDS in conjunction with other variables. (7)(8)

Complete deficiency of SP-B results in lethal neonatal respiratory disease. (9) The usual phenotype is a term infant who presents with symptoms and signs of respiratory distress and diffuse lung disease radiographically, resembling RDS in preterm infants. The initial severity of lung disease can be variable, with some children having relatively mild symptoms in the first several postnatal days, while others have rapid onset of hypoxic respiratory failure progressing to the need for extracorporeal membrane oxygenation. The disease is progressive, with only transient improvement seen with surfactant replacement therapy and modest improvement with corticosteroid treatment. Death from respiratory failure usually occurs within 3 to 6 months despite maximal medical therapy, and lung transplantation is currently the only effective treatment option. (10)(11) The disease is extremely rare, although the exact incidence is unknown.

As an autosomal recessive disorder, mutations on both alleles are necessary for an infant to be affected by SP-B deficiency. One particular frameshift mutation (121ins2) has been identified in multiple unrelated patients who have the disorder. Approximately 1 in 1,000 individuals of Northern European descent are carriers for this mutation, which has accounted for approximately 60% to 70% of the mutant *SFTPB* alleles identified to date and likely has a common ancestral origin (founder effect). (12)(13) Multiple other mutations, including a large deletion, have been identified, all of which may be categorized as loss-of-function mutations. (10)(11) (14)(15) Some mutations allow for production of proSP-B that is unable to be processed efficiently to mature SP-B, resulting in marked reduction or complete absence of mature SP-B. Those children who have mutations that allow for some SP-B production (partial deficiency) can survive well beyond the neonatal period, although they are the exception. (16)(17) Transient deficiency in association with a mutation on only one allele also has been recognized. (18) These observations, along with experiments using genetically engineered
mice in which SP-B production can be shut off, indicate that a critical level of SP-B expression is needed for normal lung function. (19) Thus, individuals whose ability to produce SP-B is impaired due to genetic mechanisms, either because of a loss-of-function mutation on one allele or more common variants associated with decreased SP-B gene expression, may be at higher risk for lung disease if other factors, such as prematurity or inflammation, further limit their SP-B production. SP-B is, therefore, a reasonable candidate gene for susceptibility to neonatal RDS as well as lung injury later in life.

Surfactant isolated from the lungs of SP-B-deficient infants is abnormal in composition and is ineffective in lowering surface tension. (20) Incomplete processing of SP-C from its precursor protein to the mature form results in the secretion of large amounts of partially processed SP-C intermediates with hydrophilic epitopes. (11) Accordingly, surfactant from SP-B-deficient infants is lacking in mature SP-C, and because the partially processed intermediates are not very surface-active, they also inhibit its function. (21) Phospholipid composition also is altered, with decreased amounts of PC and even more so of phosphatidylglycerol (PG). (20) Such secondary alterations may be related to changes within the SP-B-deficient type II cell, which lacks normal lamellar bodies and contains disorganized, poorly lamellated vesicular inclusions. (22) The lack of normally formed lamellar bodies may account for the incomplete processing of SP-C as the final steps occur in lamellar bodies. These observations indicate a fundamental intracellular role for SP-B (or proSP-B) in lamellar body biogenesis and surfactant packaging and at least partly explain the refractory nature to therapy. Incompletely processed SP-C may be a useful biomarker for diagnosis, but the sensitivity and specificity of such testing are currently unknown, and analyses are confined to research laboratories.

**Genetic Lung Disease Due to ATP-binding Cassette Protein Member 3 (ABCA3) Deficiency**

ABCA3 is a member of the ABC family of transporters, transmembrane proteins that hydrolyze adenosine triphosphate to move substrates across biologic membranes. The protein is comprised of 1,704 amino acids and contains 12 membrane-spanning domains and two nucleotide-binding domains. ABCA3 mRNA is expressed in many tissues, including brain and kidney. In the lungs, it is expressed primarily in type II cells, with the protein localized to the limiting membranes of lamellar bodies. (23) Other members of the ABCA subfamily are involved in lipid transport, and mutations in ABC genes are frequent causes of human genetic diseases. For example, ABCA1 transports cholesterol, and its gene is mutated in Tangier disease; ABCA4 transports phosphatidylethanolamine, and its gene is mutated in a form of retinal degeneration; and ABCC7 is also known as CFTR, the gene mutated in cystic fibrosis. ABCA3 deficiency now has been recognized as the cause of lung disease in both newborns who have an RDS-like phenotype and older children and adults who have forms of interstitial lung disease (ILD). (24)(25)(26)

ABCA3 is located on chromosome 16, spans more than 60,000 bases, and contains 30 coding exons. More than 90 different mutations have been reported in ABCA3, distributed among all of the coding exons. Most mutations are “private” and unique to a given family, and the degree of allelic heterogeneity has important implications for diagnostic genetic testing because sequencing of all coding exons is needed to identify affected patients. ABCA3 deficiency is an autosomal recessive disorder. However, patients have been identified who have a consistent phenotype and typical lung histopathology findings but only one identifiable mutation. (25)(26)(27) Such patients may have functionally significant mutations in untranslated regions that were not examined or could have major deletions, insertions, or rearrangements of ABCA3 that would not be detected by usual approaches. Therefore, the sensitivity of genetic testing is less than 100% for all ABCA3 mutations.

Neonates who have ABCA3 deficiency may present identically as those who have SP-B deficiency, exhibiting signs and symptoms of respiratory distress, pulmonary hypertension, diffuse infiltrates radiographically, rapid progression to hypoxemic respiratory failure, and death despite maximal medical therapy. Although initial studies focused on identifying ABCA3 mutations in newborns who had very severe disease, more recent experience indicates that the course of infants who have ABCA3 deficiency is much more variable than that seen with those who have SP-B deficiency. Affected infants who have severe initial lung disease may show gradual improvement and can be discharged from the hospital, although symptoms and signs of lung disease usually persist. Some affected infants have very mild or even no lung disease as neonates, presenting later with nonspecific findings, including failure to thrive and digital clubbing along with pulmonary signs and symptoms and a diagnosis of ILD. The finding of the same mutation, a substitution of valine for glutamic acid in codon 292 (E292V), in multiple unrelated older patients who have ILD suggests a genotype-phenotype correlation. (25)
Children who have milder forms of ABCA3 deficiency may have mutations that allow for some ABCA3 function, although this hypothesis has yet to be tested formally. Disease results from loss-of-function mutations leading to absent or decreased ABCA3 expression, abnormal trafficking of ABCA3 within the type II cell, or decreased functional activity of ABCA3. (24)(28)(29) Because many affected children have mutations other than those that would be predicted to preclude ABCA3 expression completely, therapies that improve trafficking of misfolded proteins through the endoplasmic reticulum or augment residual ABCA3 function may be of benefit. Glucocorticoids have been shown to increase ABCA3 expression in vitro, (30) although clinical studies assessing their efficacy for this disorder have not been performed.

The precise role of ABCA3 in the lung and in surfactant metabolism is unknown. Because ABCA proteins transport lipids, ABCA3 may act by transporting lipids essential for surfactant function, such as DSPC, into lamellar bodies. Analysis of lung fluid obtained at the time of lung transplantation in infants subsequently demonstrated to be ABCA3-deficient revealed marked decreases in both DSPC and PG, consistent with this hypothesis. (31) The surface tension-lowering ability of the surfactant material isolated from ABCA3-deficient children was markedly reduced compared with material obtained from control infants transplanted for pulmonary vascular disease or SP-B deficiency, which supports a lack of functional surfactant as important in the pathophysiology of the lung disease resulting from ABCA3 deficiency. (31) Although not a uniform finding, reduced amounts of SP-B and impaired processing of proSP-B to mature SP-B have been observed in association with ABCA3 deficiency, both in human infants and in a mouse model, which may aggravate surfactant deficiency further. (24)(25)(32) A role for ABCA3 in lamellar body biogenesis is supported by electron microscopic findings in affected infants. Normal lamellar bodies are absent or markedly reduced in number; instead, small, dense bodies that have eccentrically placed very electron-dense cores (giving a “fried-egg” appearance) are found in the cytoplasm of type II cells. (22)(24)(26)

An estimate of the incidence of ABCA3 deficiency is not available at this time. Given the relative frequency with which this condition has been recognized since its initial description compared with SP-B deficiency, it is probably the most common genetic cause of surfactant deficiency. The population frequency of the ABCA3 E292V mutation recently was estimated at 1 in 275 individuals in two populations. (33) Because this mutation has accounted for fewer than 10% of the mutant ABCA3 alleles identified to date, the contribution of ABCA3 sequence variants to lung disease may be substantial. Interestingly, the E292V mutation was enriched in a cohort of relatively mature (≥28 weeks’ gestation) infants who had RDS compared with controls, and in a different study, a specific ABCA3 haplotype was associated with RDS risk. (33)(34) These findings support the hypothesis that ABCA3 variants may influence the risk for RDS in preterm infants.

Genetic Lung Disease due to SP-C Gene (SFTPC) Mutations

Respiratory symptoms due to mutations in SFTPC usually do not present in neonates. Affected infants are less likely to be encountered by neonatologists than those who have SFTPB or ABCA3 mutations. The first reported patient who had an SFTPC mutation was evaluated at birth due to a family history of ILD, but was not recognized to be symptomatic until 6 weeks of age. (35) Mice engineered to be SP-C-deficient do not exhibit lung disease at birth, suggesting that SP-C is not critical for perinatal adaptation, although SP-C-deficient mice do develop lung disease with increasing age in a strain-dependent manner. (36) However, the presentation and natural history of patients who have SFTPC mutations is highly variable and includes newborns who have severe, rapidly evolving respiratory distress as well as adults who experience the onset of ILD in the fifth or sixth decade. (37) The highly variable natural history of the disorder complicates interpretation of single-patient studies of therapeutic interventions, such as therapeutic whole lung lavage and hydroxychloroquine. (38)(39) Lung transplantation may be considered in cases of severe progressive disease.

SP-C is encoded by a single small gene containing 6 exons located on the short arm of chromosome 8. The primary translation product, proSP-C, undergoes extensive proteolysis to form the 35-amino acid hydrophobic mature SP-C molecule that is encoded in exon 2 of the gene. Most mutations identified to date are located in the region of the gene encoding the carboxyterminal portion of proSP-C and only rarely involve the mature peptide domain. A substitution of threonine for isoleucine in codon 73 (173T) is the most commonly found mutation. (38)(40) In contrast to SP-B and ABCA3 deficiencies, a mutation on one allele can result in lung disease, and familial cases exhibit an autosomal dominant pattern of inheritance. Sporadic disease also may occur as the result of apparent spontaneous de novo mutations in the SP-C gene. (38)(40)
The pathophysiology of lung disease due to \textit{SFTPC} mutations is complex and incompletely understood. \textit{SFTPC} mutations are believed to result in misfolded proSP-C, which can elicit the unfolded protein response and accumulate in the endoplasmic reticulum of the type II cells, resulting in cellular stress and apoptosis in a toxic gain-of-function mechanism. (41)(42)(43) Alternatively, misfolded proSP-C may be targeted for degradation, and as proSP-C self-aggregates within the secretory pathway, causes wild type proSP-C to be degraded as well, resulting in SP-C deficiency by a dominant negative mechanism. (41)(42)(43)(44) Whether the specific mutation determines which mechanism occurs in a given patient or each can occur at different times in the same individual, depending on the degree of SP-C gene expression and other genetic and environmental factors, is unknown. The severity of lung disease cannot be predicted by the specific \textit{SFTPC} mutation. Relatives of affected individuals may carry the same mutation and remain asymptomatic. \textit{ABCA3} may act as a disease-modifying gene in this disorder, as indicated by infants heterozygous for both an \textit{ABCA3} gene mutation and the \textit{SFTPC} I73T mutation having more severe lung disease than family members who had the I73T mutation and were not carriers for an \textit{ABCA3} mutation. (45)

**Pathology**

Lung histopathology findings in patients who have \textit{SFPTB}, \textit{ABCA3}, and \textit{SFTPC} mutations may include nonspecific changes of lung injury due to prolonged mechanical ventilation and exposure to hyperoxia. More characteristic findings include marked type II cell hyperplasia, foamy macrophages in the airspaces, and accumulation of granular, proteinaceous material in the distal airspaces (Fig. 1). (9)(11)(26)(38)(46) The latter finding is similar to that observed in adult patients who have alveolar proteinosis, a disorder caused by accumulation of surfactant due to impaired macrophage function as a result of autoantibodies directed against granulocyte-macrophage colony-stimulating factor. (47) Although the term “congenital alveolar proteinosis” has been used to characterize these disorders, this terminology is potentially misleading. The amount of proteinosis material observed varies and may even be absent, proteinosis is not specific for the underlying gene disorder, and the mechanisms for proteinosis differ from those in adults. The term “surfactant dysfunction” has been used to encompass all three disorders related to genetic mechanisms disrupting surfactant function, which cannot be distinguished from one another on the basis of routine histopathology alone. (48) Specific immunohistochemical stains may provide additional information but currently are available primarily on a research basis. (11)(24)(25) Electron microscopic findings (Fig. 2) can distinguish between SP-B and ABCA3 deficiency and may be diagnostic, and such studies should be performed on lung tissue obtained by

![Figure 1. Histopathology of neonatal lung. A. Normal neonatal lung histology with thin alveolar septa and airspaces devoid of debris. B. Histopathology of the lung from a child who had fatal SP-B deficiency demonstrates thickened alveolar septa and eosinophilic, lipoproteinaceous material intermixed with large foamy alveolar macrophages (arrow) filling the alveolar spaces. C. Histopathology of the lung from a child who had fatal ABCA3 deficiency is similar to that for fatal SP-B deficiency, as shown in panel B. Original magnification is ×10.](http://neoreviews.aappublications.org)

![Figure 2. Electron microscopy of lamellar bodies in human alveolar type II cells. A. Well-developed, mature lamellar bodies (arrows) are found in alveolar type II cells from a normal lung. B. Large, disorganized, multivesicular bodies (arrows) are observed in alveolar type II cells from the lung of a child who had SP-B deficiency. C. Small, dense bodies that have eccentrically placed, electron-dense inclusions, and tightly packed phospholipid lamellae (arrows) are observed in the alveolar type II cells from the lung of a child who has ABCA3 deficiency. For panels A and B, original magnification is ×5,000; for panel C, original magnification is ×10,000.](http://neoreviews.aappublications.org)
biopsy or autopsy from infants suspected of having one of these disorders. (22)(24)(26)

Other Genetic Causes of Surfactant Dysfunction

Haploinsufficiency for the gene encoding TTF-1, either as a result of gene deletion or loss-of-function mutations on one allele, can cause a syndrome whose manifestations include neonatal respiratory distress, recurrent pulmonary infection, hypothyroidism, and neurologic symptoms. (49) Because TTF-1 is an important regulator of SP-A, SP-B, and SP-C expression, neonatal lung disease could result from delayed expression of SP-B and SP-C and chronic lung disease from reduced expression of all three proteins. However, neurologic disease (benign familial chorea) in the absence of any pulmonary disease also has been observed in association with TTF-1 haploinsufficiency.

Children who have a phenotype consistent with an inherited surfactant disorder but in whom no causative mutations in SFTPB, ABCA3, or SFTPC were found have been reported, suggesting that mutations in other genes in the surfactant metabolic pathway can result in a similar phenotype. (26)(27)(48) Candidate genes include those encoding SP-A and SP-D and the enzymes needed to process proSP-B and proSP-C to their mature forms. Mice engineered to lack expression of SP-D develop lipid accumulations and emphysema. (50) These changes were observed starting at about 3 weeks after birth and progressed with age, suggesting that human disease due to SP-D deficiency may be unlikely to present in the neonatal period. Napsin A and cathepsin H are enzymes expressed in type II pneumocytes that have potential roles in the processing of SP-B. (51)(52) Mutations in the genes encoding these proteins that disrupt their function might alter surfactant composition and lead to dysfunction and lung disease in the newborn period.

Diagnostic Evaluation

It is not possible to distinguish genetic causes of surfactant deficiency from treatable or transient causes of neonatal respiratory disease such as RDS, retained fetal lung fluid syndrome, or pneumonia purely on clinical or radiographic grounds. A lack of risk factors for RDS or infection in a child who has diffuse parenchymal lung disease should raise suspicion for an inherited surfactant disorder, and a family history of severe neonatal lung disease should prompt evaluation. Disease due to SP-B deficiency is relentlessly progressive; disease due to ABCA3 deficiency may improve, but the symptoms usually do not resolve and radiographs do not clear completely. Newborns who have SFTPC mutations may show substantial improvement either with treatment or as a result of the natural history of the disease. In general, the longer that respiratory symptoms and diffuse radiographic changes persist without a cause established, the higher the likelihood of an inherited surfactant disorder.

Analysis of lung fluid samples for surfactant components currently is only available in research laboratories. The sensitivity and specificity of such testing is unknown, both for distinguishing inherited surfactant disorders from other diseases and for indicating which gene is responsible. Genetic analyses provide the most definitive means for establishing a specific diagnosis, and sequence analysis of all of the coding exons of SFTPB, ABCA3, and

Figure 3. Algorithm for genetic testing in term infants who have respiratory failure of unknown cause and a suspected inherited surfactant disorder as the cause. In babies of Northern European descent, screening first for the SFTPB 121ins2 mutation may allow for rapid diagnosis. If such test results are negative or the child is of a different ethnic background, sequencing studies are needed. SFTPC should be evaluated in children who have a consistent phenotype in whom studies for SFTPB and ABCA3 are negative or in whom only one ABCA3 mutation is identified. +/- = heterozygous. SMDP = surfactant metabolism dysfunction, pulmonary.
SFTPC is available through certified diagnostic laboratories in the United States and Europe. A positive result may obviate the need for lung biopsy. Limitations to genetic testing include cost and long turnaround times in critically ill or rapidly deteriorating infants for whom a timely diagnosis is needed for management decisions. The interpretation of genetic studies also may be difficult, particularly when rare missense variants not previously known to be associated with lung disease are found, or if an SFTPB or ABCA3 mutation is identified on only one allele.

Although genetic testing is not inexpensive (currently approximately United States $4,000 for all three genes), its costs, both in dollars as well as risks to the patient, should be kept in perspective relative to those of performing a lung biopsy and of prolonged intensive care. A sequential approach to genetic studies may be reasonable, screening first for the SFTPB 121ins2 mutation in babies of Northern European descent, given its prevalence in this subpopulation, followed by sequence analysis for ABCA3 and SFTPC mutations (Fig. 3). If results of such studies are negative and the index of suspicion remains high for a surfactant metabolic disorder, studies for SFTPC mutations can be obtained. Children who present with lung disease after the neonatal period should be evaluated initially for SFTPC mutations and subsequently for ABCA3 mutations if initial study results are unrevealing. SP-B deficiency is very unlikely in children presenting beyond the neonatal period, and testing for SFTPB mutations is unlikely to be revealing and not cost-effective in older children, with very rare exceptions. Finally, in cases where results of genetic studies are unrevealing or ambiguous or when a more immediate diagnosis is needed, lung biopsy may be indicated. Guidelines for the handling and processing of such tissue have been published. (53) In addition to routine histologic studies, tissue should be prepared for electron microscopy.

**Summary**

Inherited surfactant disorders are rare but important causes of neonatal mortality and morbidity. Considerable clinical overlap exists among the three known single-gene disorders, with the spectrum of disease ranging from severe neonatal respiratory failure to chronic respiratory symptoms in older children and adults; salient features are summarized in the Table. These disorders have provided insights into normal surfactant metabolism and indicated that these genes may be involved in more common lung diseases, such as RDS and bronchopulmonary dysplasia. Mutations in genes encoding other proteins important in surfactant function and metabolism may result in similar disease pictures.

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**Table. Inherited Surfactant Deficiency Disorders**

<table>
<thead>
<tr>
<th>OMIM</th>
<th>SMDP1 #265120</th>
<th>SMDP2 #610913</th>
<th>SMDP3 #610921</th>
</tr>
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<tbody>
<tr>
<td><strong>Locus</strong></td>
<td>SFTPB</td>
<td>SFTPC</td>
<td>ABCA3</td>
</tr>
<tr>
<td><strong>Chromosomal location</strong></td>
<td>2p12–p11.2</td>
<td>8p21</td>
<td>16p13.3</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>SP-B</td>
<td>SP-C</td>
<td>ABCA3</td>
</tr>
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<td>Autosomal dominant or sporadic</td>
<td>Autosomal recessive</td>
</tr>
<tr>
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<td>Dominant negative or toxic gain-of-function</td>
<td>Loss-of-function</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
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<td>Infancy to adult &gt; Neonatal</td>
<td>Neonatal &gt; Childhood</td>
</tr>
<tr>
<td><strong>Clinical Syndrome</strong></td>
<td>RDS</td>
<td>ILD &gt; RDS</td>
<td>RDS or ILD</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Fatal without transplant</td>
<td>Variable</td>
<td>Severe variable</td>
</tr>
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</table>


5. Pulmonary surfactant is a mixture of lipids and specific proteins that reduces surface tension at the air-liquid interface and prevents end-expiratory atelectasis of the lung. Of the following, the principal constituent of surfactant needed for lowering surface tension is:

A. Cholesterol.
B. Phosphatidylcholine.
C. Phosphatidylethanolamine.
D. Phosphatidylglycerol.
E. Sphingomyelin.

6. Surfactant protein B (SP-B) is a low-molecular weight, hydrophobic protein that facilitates the adsorption of surfactant lipids to the air-liquid interface after secretion, essential for surface tension-lowering properties of the surfactant. Genetic lung disease from SP-B deficiency is a rare, autosomal recessive disorder that results in progressive hypoxemic respiratory failure and death by 3 to 6 months of age. Of the following, the most common genetic mutation related to the SP-B gene in infants of Northern European descent involves:

A. Frameshift mutation (121ins2).
B. Nucleotide tandem repeats in intron 4.
C. Polymorphism in exon 4.
D. Polymorphism in promoter region.
E. Thyroid transcription factor-1.

7. Adenosine triphosphate (ATP)-binding cassette (ABC) transporters are transmembrane proteins that hydrolyze ATP to move substrates across biologic membranes. Mutations in ABC genes are frequent causes of human genetic diseases. Of the following, the deficiency of ABCA3 protein is most likely to cause:

A. Cystic fibrosis.
B. Hypothyroidism.
C. Interstitial lung disease.
D. Retinal degeneration.
E. Tangier disease.

8. Surfactant protein C (SP-C) is a low-molecular weight, hydrophobic protein, derived by proteolysis of its precursor, proSP-C, the primary translational product of a gene located on chromosome 8. SP-C gene mutations can cause genetic lung disease. Of the following, the most accurate statement regarding genetic lung disease from SP-C gene mutations is that:

A. Lung histopathology reveals hypoplasia of type II alveolar epithelial cells.
B. Most familial cases exhibit an autosomal recessive pattern of inheritance.
C. Most mutations occur in the carboxy-terminal portion of proSP-C.
D. Respiratory symptoms typically manifest in the perinatal period.
E. Severity of lung disease can be predicted by specific SP-C gene mutations.