



Disease Information

Pulmonary surfactant is a mixture of lipids and proteins lining the surface of the lungs that facilitates air exchange. Surfactant proteins are critical for pulmonary health as they manage infectious challenges and the biomechanical stresses of oxygen exchange on the lung tissue. Defects in production, processing, and transport of surfactant components have been associated with a wide range of diagnoses.^{1,2} Genetic testing for defects in three genes (*SFTPB*, *SFTPC*, and *ABCA3*) is a useful and efficient diagnostic tool for the investigation of severe neonatal respiratory distress and interstitial lung diseases.

Surfactant Protein B (SP-B) has a critical role in stabilizing and enhancing rapid spreading of the surfactant phospholipid layer to reduce surface tension in the alveoli. Inherited Surfactant Protein B Deficiency is caused by autosomal recessive mutations of the *SFTPB* gene that result in atelectasis and respiratory failure in full-term infants. Rare cases of SP-B mutations resulting in severe disease with longer survival have been reported.³ Lung fluid and tissues of affected patients exhibit reduced or absent SP-B, accumulation of abnormal Surfactant Protein C precursor, and pulmonary alveolar proteinosis.

Surfactant Protein C (SP-C) has a similar role in reducing surface tension. Defects in SP-C's *SFTPC* gene can manifest as one of many different diagnoses across a wide range of onset ages, even within the same family. SP-C related disease has presented as chronic or nonspecific interstitial pneumonitis in infancy and childhood, as the usual and desquamative types of interstitial pneumonitis in early through late adulthood, and as other types of interstitial lung disease (ILD).⁴⁻⁶ Familial cases with dominant inheritance of mutations and sporadic cases with *de novo* mutations have been described.^{5,6}

ABCA3 protein is involved in the formation of lamellar bodies which transport surfactant phospholipids and proteins from their production site to the alveolar space.⁷ Clinical and histological presentation of *ABCA3* gene mutations may be similar to that of either SP-B or SP-C deficiencies. Mutations are typically inherited in an autosomal recessive pattern and are a significant cause of both neonatal respiratory failure⁸ and pediatric ILD.⁹

Research on the interactions of these genes is unfolding. The co-occurrence of a heterozygous *ABCA3* mutation and the *SFTPC* mutation 173T in three infantile-onset pediatric ILD patients whose asymptomatic parents each carried only one of the two mutations suggests *ABCA3* mutations may modify the severity of the *SFTPC* mutation.¹⁰

Testing Benefits & Indications

DNA sequence analysis of surfactant genes provides the following advantages over other diagnostic tests:

- results are not affected by prematurity or the disease process
- done on easily-collected whole blood, bloodspot, or saliva sample
- enables appropriate counseling of patients and family members

Clinical indications for testing are:

- respiratory failure in full-term newborns (*SFTPB*, *ABCA3*)
- chronic respiratory distress after the newborn period (*SFTPB*, *SFTPC*, *ABCA3*)
- pediatric interstitial disease, especially chronic pneumonitis of infancy (CPI), desquamative interstitial pneumonitis (DIP), and non-specific interstitial pneumonitis (NSIP) (*SFTPC*, *ABCA3*)
- adult interstitial lung disease with family history (*SFTPC*, *ABCA3*), including pulmonary fibrosis (*SFTPC*)
- follow-up to abnormal histology or BAL/tracheal aspirate analysis (*SFTPB*, *SFTPC*, *ABCA3*)
- carrier screening in parents of full-term newborn with unexplained respiratory failure (*SFTPB*, *ABCA3*)

Test Description

Tests for each of the genes may be ordered separately, concurrently, or in sequence according to the physician's preference. Each test is a full-gene sequence analysis of all translated regions of the SFTPB, SFTPC, or ABCA3 gene. PCR-based double-stranded automated sequencing is performed in the sense and antisense directions for the following exons of the requested gene, plus at least 20 bases into the 5' and 3' ends of all the related introns: the 10 translated exons (1 through 10) of the SFTPB gene's 11 exons, the 5 translated exons (1 through 5) of the SFTPC gene's 6 exons, or the 30 translated exons (4 through 33) of the ABCA3 gene's 33 exons.

Specific mutation analysis for individual SFTPB, SFTPC, and ABCA3 mutations known to be in the family is also available.

Mutation Detection Rate

Approximately 99% of known mutations in each gene are detectable by the corresponding test.

Turn-Around-Time

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| Gene sequence analysis, SFTBP or SFTPC..... | 5 – 10 days |
| Gene sequence analysis, ABCA3..... | 7 – 14 days |
| Specific mutation analysis, any genes..... | 5 – 10 days |

Specimen Requirements

Blood: Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

Blood Spot: Minimum of one complete spot approximately 0.5 inch in diameter on S&S 903 collection paper or similar. Store in a clean plastic bag at room temperature. Ship at room temperature.

Saliva: Collect 2 ml into Oragene™ DNA Self-Collection container. Store and ship at room temperature.

DNA: Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

Prenatal: Prenatal testing is available for the indication Surfactant deficiency. Please call an Ambry Genetic Counselor to discuss your case.

CPT Codes

Full gene analysis or specific mutation analysis of each gene.....83891, 83894, 83898, 83904, 83909, 83912

References

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