Surfactant Dysfunction Panel

Disorder also known as: Surfactant deficiency; Surfactant metabolism dysfunction; Interstitial lung disease (ILD); Pulmonary alveolar proteinosis (PAP); Neonatal respiratory failure; Postnatal respiratory distress

Panel Gene List: ABCA3, CSF2RA, CSF2RB, SFTPB, SFTPC

Clinical Features:
Genetic disorders of surfactant deficiency and metabolism dysfunction are lung disorders with clinical presentations ranging from neonatal respiratory failure to childhood- or adult-onset interstitial lung disease (ILD). Pulmonary surfactant is a mixture of lipids and proteins that line the inner surface of the lungs, reducing surface tension and preventing lung collapse.\textsuperscript{1,2} Surfactant is produced in the alveoli, tiny air sacks in the lungs where exchange of oxygen and carbon dioxide occurs. Although normal surfactant must be present to facilitate breathing, surfactant build up can block air from entering the alveoli resulting in hypoxemic respiratory failure.\textsuperscript{2} Surfactant dysfunction disorders can result from problems in production, processing, transport, and clearance of surfactant components.\textsuperscript{1,2} The signs and symptoms of surfactant dysfunction can vary in severity. The most severe form causes respiratory distress syndrome in the neonatal period, where shortly after birth, affected infants have extreme difficulty breathing. The subsequent lack of oxygen can damage the infant’s brain and other organs and most infants with this form of surfactant dysfunction do not survive longer than a few months.\textsuperscript{1,3,4} Less severe forms of surfactant dysfunction disorders can cause lung disease in infancy, childhood, or adulthood. Milder surfactant dysfunction disorders may include tachy dyspnea, failure to thrive, hypoxia, and repeated infections.\textsuperscript{1,5}

Genetics:
Pulmonary surfactant metabolism dysfunction disorders are genetically heterogeneous and can be inherited in an autosomal dominant, autosomal recessive or X-linked pattern. Pathogenic variants in \textit{SFTPB} cause autosomal recessive SP-B deficiency, a more severe form of surfactant dysfunction, which presents in full-term infants with unexplained respiratory distress and is fatal at 3 to 6 months of age. While multiple variant types have been reported in published literature, the c.397delCinsGAA variant is present in more than two-thirds of patients and has an allele frequency of 1 per 1,000 to 3,000 individuals.\textsuperscript{1,4,6} Pathogenic variants in \textit{SFTPB} usually cause loss-of-function or complete absence of SP-B. Milder disease with more prolonged survival has been reported in some children with variants that allow for some residual SP-B production.\textsuperscript{4} Variation in \textit{SFTPB} may also confer an increased risk for idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease in smokers.\textsuperscript{7,8}
Pathogenic variants in *SFTPBC* result in a reduction or absence of mature SP-C and the accumulation of abnormal SP-C. Lung disease caused by pathogenic variants in *SFTPBC* is inherited in an autosomal dominant manner with variable expressivity and reduced penetrance. The phenotype associated with *SFTPBC* pathogenic variants is variable, including neonatal forms with early mortality, childhood and adult forms with chronic respiratory disease, and asymptomatic adult carriers. Pathogenic variants in the BRICHOS domain of the protein are often associated with an earlier, more severe presentation. Missense variants account for the majority of published variants in the *SFTPBC* gene. Heterozygosity for an *ABCA3* pathogenic variant may modify the severity of lung disease associated with *SFTPBC* variants.

Pathogenic variants in *ABCA3* are associated with autosomal recessive surfactant dysfunction that can present as lethal neonatal respiratory distress as well as pediatric and adult ILD. Genotype-phenotype correlation suggests homozygous or compound heterozygous frameshift and/or nonsense pathogenic variants are associated with the most severe phenotype, whereas individuals with other variant types are more variable and less predictable. Additionally, literature suggests that heterozygous *ABCA3* variants may increase the risk for nonlethal neonatal respiratory distress syndrome.

Pathogenic variants in *CSF2RA* and *CSF2RB* lead to hereditary pulmonary alveolar proteinosis (PAP), a recessive disorder caused by an accumulation of surfactant in the lungs resulting in progressive respiratory insufficiency. *CSF2RA* is located in the pseudo-autosomal regions of the X and Y chromosomes, and pathogenic variants are more commonly found in *CSF2RA* than *CSF2RB*. Reported variants in the *CSF2RA* gene include single nucleotide variants as well as copy number variants, while only missense and frameshift variants have been reported in the *CSF2RB* gene.

**Test Methods:**
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Only sequencing analysis was performed for *SFTPBC*. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.
The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Clinical Sensitivity:
Genetic disorders of surfactant deficiency and metabolism dysfunction are rare, and the clinical sensitivity for the associated genes is not well defined. SP-B deficiency has an estimated incidence of 1 in 1 million live births in the United States. Surfactant dysfunction due to SFTPC and ABCA3 is thought to be less common than SFTP-B-related surfactant dysfunction. Hereditary PAP accounts for less than 1% of PAP, with the majority of PAP being autoimmune or secondary to other underlying diseases.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA3</td>
<td>ATP-BINDING CASSETTE SUB-FAMILY A MEMBER 3</td>
<td>AD/AR</td>
<td>Surfactant Metabolism Dysfunction, ILD</td>
</tr>
<tr>
<td>CSF2RA</td>
<td>GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR RECEPTOR SUBUNIT ALPHA</td>
<td>XL</td>
<td>PAP</td>
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<tr>
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<td>AR</td>
<td>PAP</td>
</tr>
<tr>
<td>SFTPB</td>
<td>SURFACANT PROTEIN-B</td>
<td>AR</td>
<td>Surfactant Metabolism Dysfunction</td>
</tr>
<tr>
<td>SFTP C</td>
<td>SURFACANT PROTEIN-C</td>
<td>AD</td>
<td>Surfactant Metabolism Dysfunction</td>
</tr>
</tbody>
</table>

Abbreviations: AD – Autosomal Dominant, AR – Autosomal Recessive, ILD – Interstitial Lung Disease, PAP – Pulmonary Alveolar Proteinosis, XL – X-Linked

References:


