Neonatal Respiratory Distress – Surfactant Dysfunction Panel

Test code: PU0501

Is ideal for patients with clinical respiratory distress of unknown origin and those with a suspicion of surfactant metabolism dysfunction.

Pathogenic germline mutations in several genes involved in surfactant metabolism can cause clinical features of respiratory distress syndrome (RDS) in term neonates, children and adults, disorders referred to as 'surfactant metabolism dysfunction'. Chronic respiratory distress with surfactant metabolism deficiency has autosomal dominant inheritance. Congenital alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) is caused by autosomal dominant mutations in FOXP1 and leads to neonatal respiratory distress and is thus included in the panel.

About Neonatal Respiratory Distress – Surfactant Dysfunction

The main cause of respiratory distress syndrome (RDS) in premature infants is a developmental deficiency of pulmonary surfactant. The symptoms usually appear shortly after birth and may include tachypnea, tachycardia, chest wall retractions (recession), expiratory grunting, nasal flaring and cyanosis during breathing efforts. The frequency of RDS is inversely proportional to gestational age. However, disorders of surfactant metabolism can cause RDS in neonates of all gestational ages. The severity of the disease is dependent on the mutation type. In general, surfactant protein B deficiency causes a severe and often fatal lung disease but problems from surfactant protein C deficiency can occur as late as in adulthood. Congenital alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) is caused by two broad types of genetic abnormality: mutations in FOXP1 or other genetic abnormalities such as deletions in areas of chromosome 16 that regulate the expression of FOXP1. These abnormalities are estimated to be found in 80-90% of infants with confirmed ACDMPV. Alveolar capillary dysplasia (ACD, also congenital alveolar dysplasia) is a very rare congenital malformation involving abnormal development of the capillary vascular system around the alveoli of the lungs. It is a rare cause of persistent pulmonary hypertension in infants and may also be a rare cause of pulmonary hypoplasia. ACDMPV is characterized histologically by failure of formation and ingrowth of alveolar capillaries that then do not make contact with alveolar epithelium, medial muscular thickening of small pulmonary arterioles with muscularization of the intra-acinar arterioles, thickened alveolar walls, and anomalously situated pulmonary veins running alongside pulmonary arterioles and sharing the same adventitial sheath. The disorder is associated with persistent pulmonary hypertension of the neonate and shows varying degrees of lability and severity. Babies with ACD may appear normal at birth but develop respiratory distress with persistent pulmonary hypertension within minutes or hours after birth. ACD does not respond to standard therapies that resolve simple pulmonary hypertension, and this lack of response is an essential diagnostic clue.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Neonatal Respiratory Distress – Surfactant Dysfunction Panel and their clinical significance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated phenotypes</th>
<th>Inheritance</th>
<th>ClinVar</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA3</td>
<td>Interstitial lung disease, Surfactant metabolism dysfunction, pulmonary</td>
<td>AD/AR</td>
<td>11</td>
<td>287</td>
</tr>
<tr>
<td>FOXP1</td>
<td>Alveolar capillary dysplasia with misalignment of pulmonary veins</td>
<td>AD</td>
<td>10</td>
<td>102</td>
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<tr>
<td>NKX2-1</td>
<td>Thyroid cancer, nonmedullary, Choreoathetosis, hypothyroidism, and neonatal respiratory distress, Chorea, hereditary benign</td>
<td>AD</td>
<td>27</td>
<td>137</td>
</tr>
<tr>
<td>SFTPB</td>
<td>Surfactant metabolism dysfunction, pulmonary</td>
<td>AR</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>SFTPC</td>
<td>Surfactant metabolism dysfunction, pulmonary</td>
<td>AD</td>
<td>8</td>
<td>82</td>
</tr>
</tbody>
</table>

https://blueprintgenetics.com/
*Some regions of the gene are duplicated in the genome leading to limited sensitivity within the regions. Thus, low-quality variants are filtered out from the duplicated regions and only high-quality variants confirmed by other methods are reported out. [Read more.]

Gene, refers to HGNC approved gene symbol; Inheritance to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL); ClinVar, refers to a number of variants in the gene classified as pathogenic or likely pathogenic in ClinVar ([http://www.ncbi.nlm.nih.gov/clinvar/](http://www.ncbi.nlm.nih.gov/clinvar/)); HGMD, refers to a number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD, [http://www.hgmd.cf.ac.uk/ac/](http://www.hgmd.cf.ac.uk/ac/)). The list of associated (gene specific) phenotypes are generated from CDG ([http://research.nhgri.nih.gov/CGD/](http://research.nhgri.nih.gov/CGD/)) or Orphanet ([http://www.orpha.net/](http://www.orpha.net/)) databases.

### Non-coding disease causing variants covered by the panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genomic location HG19</th>
<th>HGVS</th>
<th>RefSeq</th>
<th>RS-number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA3</td>
<td>Chr:16:2333457</td>
<td>c.3863-98C&gt;T</td>
<td>NM_001089.2</td>
<td>rs189077405</td>
</tr>
<tr>
<td>ABCA3</td>
<td>Chr:16:2358644</td>
<td>c.1112-20G&gt;A</td>
<td>NM_001089.2</td>
<td>rs746701685</td>
</tr>
<tr>
<td>ABCA3</td>
<td>Chr:16:2376495</td>
<td>c.-26-2A&gt;G</td>
<td>NM_001089.2</td>
<td></td>
</tr>
</tbody>
</table>

### Test performance

The Blueprint Genetics neonatal respiratory distress - surfactant dysfunction panel covers classical genes associated with Infant acute respiratory distress syndrome, chronic respiratory distress with surfactant metabolism deficiency, congenital alveolar capillary dysplasia and alveolar capillaries with vein misalignment. The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sliced from our high-quality whole exome sequencing data. Please see our sequencing and detection performance table for different types of alterations at the whole exome level (Table).

Assays have been validated for different starting materials including EDTA-blood, isolated DNA (no FFPE), saliva and dry blood spots (filter card) and all provide high-quality results. The diagnostic yield varies substantially depending on the assay used, referring healthcare professional, hospital and country. Blueprint Genetics' Plus Analysis (Seq+Del/Dup) maximizes the chance to find a molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be a cost-effective first line test if your patient's phenotype is suggestive of a specific mutation type.

### Bioinformatics

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the ‘Test limitations” section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the-art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases such as, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation software to make the process effective and efficient. For missense variants, in silico variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, the customer has an access to details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with inadequate coverage if present. This reflects our mission to build fully transparent diagnostics where customers have easy access to crucial details of the analysis process.
Clinical interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the cornerstone of clinical interpretation and resulting patient management decisions. Our classifications follow the Blueprint Genetics Variant Classification Schemes based on the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis of sequence variants is confirmation of variants classified as pathogenic or likely pathogenic using bi-directional Sanger sequencing. Variant(s) fulfilling the following criteria are not Sanger confirmed: the variant quality score is above the internal threshold for a true positive call, and visual check-up of the variant at IGV is in-line with the variant call. Reported variants of uncertain significance are confirmed with bi-directional Sanger sequencing only if the quality score is below our internally defined quality score for true positive call. Reported copy number variations with a size <10 exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene’s variation in population cohorts and detailed information about related phenotypes. We also provide links to the references used, congress abstracts and mutation databases to help our customers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification within the family. In the case of variants of uncertain significance (VUS), we do not recommend family member risk stratification based on the VUS result. Furthermore, in the case of VUS, we do not recommend the use of genetic information in patient management or genetic counseling.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Thus, our database, and our understanding of variants and related phenotypes, is growing by leaps and bounds. Our laboratory is therefore well positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

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ICD codes

Commonly used ICD-10 codes when ordering the Neonatal Respiratory Distress – Surfactant Dysfunction Panel

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>P22.0</td>
<td>Infant acute respiratory distress syndrome</td>
</tr>
<tr>
<td>J84.89</td>
<td>Chronic respiratory distress with surfactant metabolism deficiency</td>
</tr>
<tr>
<td>Q33.9</td>
<td>Congenital alveolar capillary dysplasia</td>
</tr>
<tr>
<td>J84.843</td>
<td>Alveolar capillary with vein misalignment</td>
</tr>
</tbody>
</table>
Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3μg*
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient’s name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

Resources

- Alveolar Capillary Dysplasia Association
- American Lung Association - Acute Respiratory Distress Syndrome
- GeneReviews - *NKX2-1*-Related Disorders
- GeneReviews - NKX2-1-Related Disorders
- NORD - Acute Respiratory Distress Syndrome
- NORD - Alveolar Capillary Dysplasia
- NORD - Respiratory Distress Syndrome, Infant
- Patient Info UK - Infant Respiratory Distress Syndrome