Short Rib Dysplasia / Asphyxiating Thoracic Dysplasia Panel

Test code: MA1101

Is ideal for patients with a clinical suspicion of asphyxiating thoracic dystrophy or short-rib dysplasia with or without polydactyly. The genes on this panel are included in the Comprehensive Growth Disorders / Skeletal Dysplasias and Disorders Panel.

Short-rib dysplasia (SRD) is a heterogeneous group of skeletal ciliopathies. Each of the causative genes of SRD is associated to the wide clinical variability supporting the development of NGS gene panel specifically dedicated to these cilia genes to identify mutations in this particularly heterogeneous group of disorders. Some forms of SRD are lethal in the neonatal period due to respiratory insufficiency secondary to a severely restricted thoracic cage, whereas others are compatible with life. Genetic diagnosis must be confirmed in the proband before proposing prenatal genetic testing. This panel is part of the Comprehensive Skeletal / Malformation Syndrome panel.

About Short Rib Dysplasia / Asphyxiating Thoracic Dysplasia

Short-rib dysplasia (SRD) with or without polydactyly refers to a group of autosomal recessive skeletal ciliopathies that are characterized by a constricted thoracic cage, short ribs, shortened tubular bones, and a trident aspect of the acetabular roof. SRD encompasses Ellis-van Creveld syndrome (EVC), Jeune syndrome or asphyxiating thoracic dystrophy (ATD), short rib-polydactyly syndromes (SRPS, Beemer-Langer type, Majewski type, Saldino-Noonan type, Verma-Taumoff type), and Mainzer-Saldino syndrome (MZSDS). Polydactyly is variably present, and there is phenotypic overlap in the various forms of SRDs, which differ by visceral malformation and metaphyseal appearance. Nonskeletal involvement can include cleft lip/palate as well as anomalies of major organs such as the brain, eye, heart, kidneys, liver, pancreas, intestines, and genitalia.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Short Rib Dysplasia / Asphyxiating Thoracic Dysplasia 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>CSPP1</td>
<td>Jeune asphyxiating thoracic dystrophy, Joubert syndrome</td>
<td>AR</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>DYNC2H1</td>
<td>Short -rib thoracic dysplasia with or without polydactyly type 1, Short -rib thoracic dysplasia with or without polydactyly type 3, Asphyxiating thoracic dysplasia (ATD; Jeune), SRPS type 2 (Majewski)</td>
<td>AR/Digenic</td>
<td>148</td>
<td>205</td>
</tr>
<tr>
<td>EVC</td>
<td>Weyers acrofacial dysostosis, Ellis-van Creveld syndrome</td>
<td>AD/AR</td>
<td>58</td>
<td>83</td>
</tr>
<tr>
<td>EVC2</td>
<td>Ellis-van Creveld syndrome, Weyers acroental dysostosis</td>
<td>AD/AR</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td>GLI2</td>
<td>Culler-Jones syndrome</td>
<td>AD</td>
<td>29</td>
<td>82</td>
</tr>
<tr>
<td>IFT122*</td>
<td>Sensenbrenner syndrome, Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1, Cranioectodermal dysplasia (Levin-Sensenbrenner) type 2</td>
<td>AR</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>IFT140</td>
<td>Short -rib thoracic dysplasia with or without polydactyly, Asphyxiating thoracic dysplasia (ATD; Jeune)</td>
<td>AR</td>
<td>38</td>
<td>63</td>
</tr>
<tr>
<td>IFT172</td>
<td>Retinitis pigmentosa, Short -rib thoracic dysplasia with or without polydactyly, Asphyxiating thoracic dysplasia (ATD; Jeune)</td>
<td>AR</td>
<td>22</td>
<td>25</td>
</tr>
</tbody>
</table>

https://blueprintgenetics.com/
IFT52: Short-rib thoracic dysplasia 16 with or without polydactyly, AR
IFT80: Short-rib thoracic dysplasia with or without polydactyly, Asphyxiating thoracic dysplasia (ATD; Jeune), AR
NEK1: Short-rib thoracic dysplasia with or without polydactyly, SRPS type 2 (Majewski), AR/Digenic
TCTEX1D2: Short-rib thoracic dysplasia 17 with or without polydactyly, Jeune Asphyxiating Thoracic Dystrophy, AR
TCTN3: Orofaciiodigital syndrome (Mohr-Majewski syndrome), Joubert syndrome, AR
TTC21B: Short-rib thoracic dysplasia, Nephronophthisis, Asphyxiating thoracic dysplasia (ATD; Jeune), AR
WDR19: Retinitis pigmentosa, Nephronophthisis, Short-rib thoracic dysplasia with or without polydactyly, Senior-Loken syndrome, Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1, Cranioectodermal dysplasia (Levin-Sensenbrenner) type 2, Asphyxiating thoracic dysplasia (ATD; Jeune), AR
WDR34: Short-rib thoracic dysplasia with or without polydactyly, Asphyxiating thoracic dysplasia (ATD; Jeune), AR
WDR35: Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1, Cranioectodermal dysplasia (Levin-Sensenbrenner) type 2, Short rib-polydactyly syndrome type 5, AR
WDR60: Short-rib thoracic dysplasia 8 with or without polydactyly, AR

*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/); 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/). The list of associated (gene specific) phenotypes are generated from CDG (http://research.nhgri.nih.gov/CGD/) or Orphanet (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>DYNC2H1</td>
<td>Chr11:103019205</td>
<td>c.2819-14A&gt;G</td>
<td>NM_001080463.1</td>
<td>rs781091611</td>
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<tr>
<td>DYNC2H1</td>
<td>Chr11:103055609</td>
<td>c.6478-16G&gt;A</td>
<td>NM_001080463.1</td>
<td>rs376892534</td>
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<tr>
<td>EVC</td>
<td>Chr4:5749725</td>
<td>c.940-150T&gt;G</td>
<td>NM_153717.2</td>
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</tr>
<tr>
<td>IFT122</td>
<td>Chr3:129207087</td>
<td>c.2005-13T&gt;A</td>
<td>NM_052985.3</td>
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</tr>
<tr>
<td>IFT140</td>
<td>Chr16:1576595</td>
<td>c.2577+25G&gt;A</td>
<td>NM_014714.3</td>
<td>rs1423102192</td>
</tr>
<tr>
<td>WDR35</td>
<td>Chr2:20151929</td>
<td>c.1434-684G&gt;T</td>
<td>NM_001006657.1</td>
<td></td>
</tr>
<tr>
<td>WDR35</td>
<td>Chr2:20182313</td>
<td>c.143-18T&gt;A</td>
<td>NM_001006657.1</td>
<td></td>
</tr>
</tbody>
</table>
Test performance

The Blueprint Genetics short rib dysplasia / asphyxiating thoracic dysplasia panel covers classical genes associated with short-rib dysplasia with or without polydactyly and asphyxiating thoracic dystrophy. 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 Short Rib Dysplasia / Asphyxiating Thoracic Dysplasia Panel

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q77.2</td>
<td>Short-rib dysplasia with or without polydactyly</td>
</tr>
<tr>
<td>Q77.2</td>
<td>Asphyxiating thoracic dystrophy</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

- Forgotten Diseases Research Foundation
- Jeune Syndrome Foundation
- NORD - Dystrophy, Asphyxiating Thoracic
- NORD - Ellis Van Creveld Syndrome
- Restricted Growth Association