Spondylometaphyseal / Spondyloepi-(meta)-physeal Dysplasia Panel

Test code: MA1701

The Blueprint Genetics Spondylometaphyseal / Spondyloepi-(meta)-physeal Dysplasia Panel is an 18 gene test for genetic diagnostics of patients with clinical suspicion of spondylometaphyseal or Spondyloepi-(meta)-physeal dysplasia.

Spondylometaphyseal dysplasias are a heterogeneous group of disorders associated with spondular dysplasia and metaphyseal abnormalities and this panel provides a tool for differential diagnostics and confirmation of the clinical diagnosis. This panel is part of Comprehensive Skeletal / Malformation Syndrome Panel.

About Spondylometaphyseal / Spondyloepi-(meta)-physeal Dysplasia

The spondylometaphyseal dysplasias constitute a very complex heterogeneous group of disorders. The disorders are characterized by the association of spondular dysplasia and metaphyseal abnormalities of the tubular bones and associated with walking and growth disturbances that become evident usually in early childhood. The disorders involve platyspondyly (flattened vertebrae) and marked hip and knee metaphyseal lesions. The different forms of spondylometaphyseal dysplasia are distinguished by the localization and severity of involvement of the affected metaphyses. In addition to the Kozlowski type, which is the most common form, three subgroups can be distinguished by the appearance of the femoral neck. In the first group the changes are severe with absent ossification of the femoral neck and coxa vara. In the second group the changes of the femoral neck are moderate and in the third mild metaphyseal irregularities are only visible. Spondylometaphyseal dysplasia may also occur in association with other clinical manifestations such as facial dysmorphism and dentinogenesis imperfecta.

Kozlowski type of spondylometaphyseal dysplasia results in severe kyphoscoliosis and is caused by mutations in the \textit{TRPV4} gene. It is transmitted in an autosomal dominant manner, as well as the form of spondylometaphyseal dysplasia (‘corner fracture’ or Sutcliffe type), the Algerian (or Schmidt) type and some moderate forms. Several autosomal recessive forms have also been identified, including type A4 and an axial type associated with retinitis pigmentosa and optic atrophy. Also a form of spondylometaphyseal dysplasia with X-linked transmission has been reported.

Availability

Results in 3-4 weeks. We do not offer a maternal cell contamination (MCC) test at the moment. We offer prenatal testing only for cases where the maternal cell contamination studies (MCC) are done by a local genetic laboratory. Read more: http://blueprintgenetics.com/faqs/#prenatal

Gene set description

Genes in the Spondylometaphyseal / Spondyloepi-(meta)-physeal 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>ACP5</td>
<td>Spondyloenchondrodysplasia with immune dysregulation</td>
<td>AR</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>B3GALT6</td>
<td>Spondyloepimetaphyseal dysplasia with joint laxity, Ehlers-Danlos syndrome</td>
<td>AR</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>CANT1</td>
<td>Desbuquois dysplasia</td>
<td>AR</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>CHST3</td>
<td>Spondyloepiphyseal dysplasia with congenital joint dislocations (recessive Larsen syndrome)</td>
<td>AR</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>Gene</td>
<td>Phenotypes</td>
<td>Inheritance</td>
<td>Variants</td>
<td>Affected Regions</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>COL2A1</td>
<td>Avascular necrosis of femoral head, Rhegmatogenous retinal detachment, Epiphyseal dysplasia, with myopia and deafness, Czech dysplasia, Achondrogenesis type 2, Platspondylytic dysplasia Torrance type, Hypochondrogenesis, Spondyloepiphyseal dysplasia congenital (SEDC), Spondyloepimetaepiphyseal dysplasia (SEMD) Strudwick type, Kniest dysplasia, Spondyloperipheral dysplasia, Mild SED with premature onset arthrosis, SED with metatarsal shortening, Stickler syndrome type 1</td>
<td>AD</td>
<td>106</td>
<td>537</td>
</tr>
<tr>
<td>COL11A1</td>
<td>Marshall syndrome, Fibrochondrogenesis, Stickler syndrome type 2</td>
<td>AD/AR</td>
<td>18</td>
<td>76</td>
</tr>
<tr>
<td>COL11A2</td>
<td>Weissenbacher-Zweymuller syndrome, Deafness, Otospondylomegagaphyseal dysplasia, Fibrochondrogenesis, Stickler syndrome type 3 (non-non-cular)</td>
<td>AD/AR</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td>DYM</td>
<td>Dyggve-Melchior-Clausen dysplasia, Smith-McCort dysplasia</td>
<td>AR</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>EIF2AK3</td>
<td>SED, Wolcott-Rallison type</td>
<td>AR</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>HSPG2</td>
<td>Schwartz-Jampel syndrome, Dyssegmental dysplasia Silverman-Handmaker type, Dysssegmental dysplasia Rolland-Desbuquis type</td>
<td>AD/AR</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>MATN3</td>
<td>Spondyloepimetaepiphyseal dysplasia Matrilin type, Multiple epiphyseal dysplasia type 5 (EDM5)</td>
<td>AD/AR</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>PAPSS2</td>
<td>Brachyolmia 4 with mild epiphyseal and metaphyseal changes, SEMD PAPPS2 type</td>
<td>AR</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>RMRP</td>
<td>Cartilage-hair hypoplasia, Metaphyseal dysplasia without hypotrichosis, Anauxetic dysplasia</td>
<td>AR</td>
<td>24</td>
<td>119</td>
</tr>
<tr>
<td>SLC39A13</td>
<td>Spondylo dysplastic Ehlers-Danlos syndrome</td>
<td>AR</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>SMARCAL1</td>
<td>Schimke immunoosseous dysplasia</td>
<td>AR</td>
<td>9</td>
<td>70</td>
</tr>
<tr>
<td>TRAPPC2*</td>
<td>Spondyloepiphyseal dysplasia tarda</td>
<td>XL</td>
<td>12</td>
<td>54</td>
</tr>
<tr>
<td>TRPV4</td>
<td>Metatropic dysplasia, Spondyloepiphysial dysplasia Maroteaux type, Parastremmatic dwarfism, Hereditary motor and sensory neuropathy, Spondyloepimetaepiphyseal dysplasia Kozlowski type, Spinal muscular atrophy, Charcot-Marie-Tooth disease, Brachyolmia (autosomal dominant type), Familial Digital arthropathy with brachydactyly</td>
<td>AD</td>
<td>53</td>
<td>71</td>
</tr>
<tr>
<td>WISP3</td>
<td>Arthropathy, progressive pseudorheumatoid, of childhood, Spondyloepiphyseal dysplasia tarda with progressive arthropathy</td>
<td>AR</td>
<td>13</td>
<td>68</td>
</tr>
</tbody>
</table>

*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.](https://blueprintgenetics.com/)

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.

**Test performance**

Blueprint Genetics offers a comprehensive Spondylometaphyseal / Spondyloepi-(meta)-physeal Dysplasia Panel that covers classical genes associated with spondylometaphyseal or Spondyloepi-(meta)-physeal dysplasia. The genes are carefully selected based on the existing scientific evidence, our experience and most current mutation databases. Candidate genes are excluded from this first-line diagnostic test. The test does not recognise balanced translocations or complex inversions, and it may not detect low-level mosaicism. The test should not be used for analysis of sequence repeats or for diagnosis of disorders.
caused by mutations in the mitochondrial DNA.

Analytical validation is a continuous process at Blueprint Genetics. Our mission is to improve the quality of the sequencing process and each modification is followed by our standardized validation process. Average sensitivity and specificity in Blueprint NGS Panels is 99.3% and 99.9% for detecting SNPs. Sensitivity to for indels vary depending on the size of the alteration: 1-10bps (96.0%), 11-20 bps (88.4%) and 21-30 bps (66.7%). The longest detected indel was 46 bps by sequence analysis. Detection limit for Del/Dup (CNV) analysis varies through the genome depending on exon size, sequencing coverage and sequence content. The sensitivity is 71.5% for single exon deletions and duplications and 99% for three exons’ deletions and duplications. We have validated the assays for different starting materials including EDTA-blood, isolated DNA (no FFPE) and saliva that all provide high-quality results. The diagnostic yield varies substantially depending on the used assay, referring healthcare professional, hospital and country. Blueprint Genetics' Plus Analysis (Seq+Del/Dup) maximizes the chance to find molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be cost-effective first line test if your patient’s phenotype is suggestive for a specific mutation profile.

Bioinformatics

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. The highest relevance in the reported variants is achieved through elimination of false positive findings based on variability data for thousands of publicly available human reference sequences and validation against our in-house curated mutation database as well as the most current and relevant human mutation databases. Reference databases currently used are the 1000 Genomes Project (http://www.1000genomes.org), the NHLBI GO Exome Sequencing Project (ESP; http://evs.gs.washington.edu/EVS), the Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org), ClinVar database of genotype-phenotype associations (http://www.ncbi.nlm.nih.gov/clinvar) and the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk).

The consequence of variants in coding and splice regions are estimated using the following in silico variant prediction tools: SIFT (http://sift.jcvi.org), Polyphen (http://genetics.bwh.harvard.edu/pph2/), and Mutation Taster (http://www.mutationtaster.org).

Through our online ordering and statement reporting system, Nucleus, the customer can access specific details of the analysis of the patient. This includes coverage and quality specifications and other relevant information on the analysis. This represents our mission to build fully transparent diagnostics where the customer gains easy access to crucial details of the analysis process.

Clinical interpretation

In addition to our cutting-edge patented sequencing technology and proprietary bioinformatics pipeline, we also provide the customers with the best-informed clinical report on the market. Clinical interpretation requires fundamental clinical and genetic understanding. At Blueprint Genetics our geneticists and clinicians, who together evaluate the results from the sequence analysis pipeline in the context of phenotype information provided in the requisition form, prepare the clinical statement. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals, even without training in genetics.

Variants reported in the statement are always classified using the Blueprint Genetics Variant Classification Scheme modified from the ACMG guidelines (Richards et al. 2015), which has been developed by evaluating existing literature, databases and with thousands of clinical cases analyzed in our laboratory. Variant classification forms the corner stone of clinical interpretation and following patient management decisions. Our statement also includes allele frequencies in reference populations and in silico predictions. We also provide PubMed IDs to the articles or submission numbers to public databases that have been used in the interpretation of the detected variants. In our conclusion, we summarize all the existing information and provide our rationale for the classification of the variant.

A final component of the analysis is the Sanger confirmation of the variants classified as likely pathogenic or pathogenic. This does not only bring confidence to the results obtained by our NGS solution but establishes the mutation specific test for family members. Sanger sequencing is also used occasionally with other variants reported in the statement. In the case of variant of uncertain significance (VUS) we do not recommend risk stratification based on the genetic finding. Furthermore, in the case VUS we do not recommend use of genetic information in patient management or genetic counseling. For some cases Blueprint Genetics offers a special free of charge service to investigate the role of identified VUS.
We constantly follow genetic literature adapting new relevant information and findings to our diagnostics. Relevant novel discoveries can be rapidly translated and adopted into our diagnostics without delay. These processes ensure that our diagnostic panels and clinical statements remain the most up-to-date on the market.

**CPT codes**

SEQ 81479
DEl/Dup 81479

**ICD codes**

Commonly used ICD-10 codes when ordering the Spondylometaphyseal / Spondyloepi-(meta)-physeal Dysplasia Panel

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Q77.8</td>
<td>Spondylometaphyseal or Spondyloepi-(meta)-physeal dysplasia</td>
<td></td>
</tr>
</tbody>
</table>

**Accepted sample types**

- EDTA blood, min. 1 ml
- Purified DNA, min. 5μg
- 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**

- NORD - Metaphyseal Chondrodysplasia, Schmid Type
- Gene Reviews - TRPV4-Associated Disorders