Metaphyseal Dysplasia Panel

Test code: MA2501

The Blueprint Genetics Metaphyseal Dysplasia Panel is a 10 gene test for genetic diagnostics of patients with clinical suspicion of craniometaphyseal dysplasia, metaphyseal anadysplasia, metaphyseal chondrodysplasia or metaphyseal dysplasia.

This panel covers several skeletal dysplasias (osteochondrodysplasias) characterized by metaphyseal changes in bones. Most of these dysplasias are very rare. For differential diagnosis, the most common form of chondrodysplasia, achondroplasia, is also included to the panel. This panel is part of the Comprehensive Skeletal / Malformation Syndrome panel.

About Metaphyseal Dysplasia

Metaphyseal dysplasia, also known as Pyle’s disease is a rare recessive bone dysplasia characterised by genu valgum, metaphyseal anomalies with broadening of the long bones extending into the diaphyses, widening of the ribs and clavicles, platyspondyly and cortical thinning. Differential diagnosis includes Braun-Tischert type of metaphyseal dysplasia.

Schmid type metaphyseal chondrodysplasia is a type of chondrodysplasia associated with a deficiency of COL10A1. It is characterized by short stature with short legs, bowing of the long bones, coxa vara, and waddling gait. Jansen type metaphyseal chondrodysplasia is a disease that results from ligand-independent activation of the type 1 of the parathyroid hormone receptor (PTHR1). It is a rare autosomal dominant form of short limb dwarfism characterized by asymptomatic hypercalcemia and skeletal deformities.

Metaphyseal anadysplasia is a very rare form of metaphyseal dysplasia that is characterized by short stature, rhizomelic micromelia and a mild varus deformity of the legs evident from the first months of life, that are associated with radiological features of severe metaphyseal changes in long bones, and generalized osteopenia, and that usually spontaneously resolve by the age of three years. Severe autosomal dominant and milder recessive variants have been observed in either MMP9 or MMP13.

Craniometaphyseal dysplasia is an osteochondrodysplasia characterized by hyperostosis and sclerosis of the craniofacial bones associated with abnormal modeling of the metaphyses. Sclerosis of the skull may lead to asymmetry of the mandible, as well as to cranial nerve compression, that may finally result in hearing loss and facial palsy. Autosomal dominant and autosomal recessive forms exist, with causative genes ANKH and GLA1.

Achondroplasia is characterized by rhizomelia, exaggerated lumbar lordosis, brachydactyly, and macrocephaly with frontal bossing and midface hypoplasia. Estimated incidence is at about 1/25,000 live births worldwide. Achondroplasia is due to mutations in the FGFR3 gene. Inheritance is autosomal dominant so genetic counseling is warranted. Achondroplasia is one of the congenital conditions with similar presentations, such as multiple epiphyseal dysplasia tarda, achondrogenesis, osteopetrosis, and thanatophoric dysplasia.

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated phenotypes</th>
<th>Inheritance</th>
<th>ClinVar</th>
<th>HGMD</th>
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<tbody>
<tr>
<td>ANKH</td>
<td>Calcium pyrophosphate deposition disease (familial chondrocalcinosis type 2), Craniometaphyseal dysplasia autosomal dominant type</td>
<td>AD</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>CDKN1C</td>
<td>Beckwith-Wiedemann syndrome, IMAGE syndrome</td>
<td>AD</td>
<td>25</td>
<td>79</td>
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### Test performance

Blueprint Genetics offers a comprehensive Metaphyseal Dysplasia Panel that covers classical genes associated with craniometaphyseal dysplasia, metaphyseal anadysplasia, metaphyseal chondrodysplasia and metaphyseal 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 recognize 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 Metaphyseal Dysplasia Panel

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<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
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https://blueprintgenetics.com/
### 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
- NORD - Metaphyseal Chondrodysplasia, Jansen Type
- NORD - Metaphyseal Chondrodysplasia, McKusick Type
- NORD - Craniometaphyseal Dysplasia
- Gene Reviews - Craniometaphyseal Dysplasia