Hereditary Paraganglioma-Pheochromocytoma Panel

Test code: ON1201

The Blueprint Genetics Hereditary Paraganglioma-Pheochromocytoma Panel analyzes 11 genes associated with inherited susceptibility to paragangliomas and/or pheochromocytomas.

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are predominantly autosomal dominant diseases, with few exceptions showing paternal dominant inheritance pattern. The Hereditary Paraganglioma-Pheochromocytoma Panel is suited for detecting heritable germline mutations in the clinically implicated genes and may not be used for the detection of somatic mutations in tumor tissue. This Panel is part of the Hereditary Endocrine Cancer Panel and Comprehensive Hereditary Cancer Panel.

About Hereditary Paraganglioma-Pheochromocytoma

Hereditary PGL/PCC is a genetic condition that is characterized by the presence of tumors originating from the neuroendocrine tissue. Paragangliomas are tumors that are often found in the head and neck, and are arising in the cellular structures called the paraganglia. Pheochromocytomas are located outside of the head and neck, and specifically develop in the paraganglia of the adrenal glands. Hereditary PGL/PCC patients tend to develop multifocal (multiple tumors arising from the same anatomical location) and bilateral (tumors found in symmetrical organ sites) disease. Majority of the pathogenic mutations associated with the development of PGL/PCC are found in the NF1, RET, SDHB, SDHD and VHL genes. Recently, pathogenic germline mutations in FH have been found in patients with PGL/PCC. Although most of the PGL/PCC tumors are noncancerous, individuals with pathogenic mutation in one of the tested genes are more likely to eventually develop cancer. The syndromes are characterized by reduced penetrance and the outcome varies depending on the affected gene. Prevalence of hereditary paraganglioma-pheochromocytoma is 1:100 000.

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 Hereditary Paraganglioma-Pheochromocytoma 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>FH</td>
<td>Hereditary leiomyomatosis and renal cell cancer</td>
<td>AD/AR</td>
<td>89</td>
<td>161</td>
</tr>
<tr>
<td>MAX</td>
<td>Pheochromocytoma</td>
<td>AD</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>NF1*</td>
<td>Watson syndrome, Neurofibromatosis, Neurofibromatosis-Noonan syndrome</td>
<td>AD</td>
<td>261</td>
<td>2607</td>
</tr>
<tr>
<td>RET</td>
<td>Hirschsprung disease, Central hypoventilation syndrome, congenital, Pheochromocytoma, Medullary thyroid carcinoma, Multiple endocrine neoplasia</td>
<td>AD/AR</td>
<td>80</td>
<td>405</td>
</tr>
<tr>
<td>SDHA*</td>
<td>Leigh syndrome/Mitochondrial respiratory chain complex II deficiency, Gastrointestinal stromal tumor, Paragangliomas, Dilated cardiomyopathy (DCM)</td>
<td>AD/AR</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>SDHAF2</td>
<td>Paragangliomas</td>
<td>AD</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>SDHB</td>
<td>Paraganglioma and gastric stromal sarcoma, Pheochromocytoma, Gastrointestinal stromal tumor, Paragangliomas, Cowden-like syndrome</td>
<td>AD</td>
<td>72</td>
<td>249</td>
</tr>
<tr>
<td>SDHC</td>
<td>Paraganglioma and gastric stromal sarcoma, Gastrointestinal stromal tumor, Paragangliomas</td>
<td>AD</td>
<td>14</td>
<td>53</td>
</tr>
</tbody>
</table>
**SDHD**
Paraganglioma and gastric stromal sarcoma, Pheochromocytoma, Paragangliomas, Carcinoid tumors, intestinal, Cowden syndrome  
AD  42  158

**TMEM127**
Pheochromocytoma  
AD  20  38

**VHL**
Erythrocytosis, familial, Pheochromocytoma  
AD/AR  143  573

*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>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>chr17:29577934</td>
<td>c.4110+1802delA</td>
<td>NM_001042492.2</td>
<td>rs863224944</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF1</td>
<td>chr17:29657848</td>
<td>c.5812+332A&gt;G</td>
<td>NM_001042492.2</td>
<td>rs863224491</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMEM127</td>
<td>chr2:96931137</td>
<td>c.-18C&gt;T</td>
<td>NM_017849.3</td>
<td>rs121908813</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VHL</td>
<td>chr3:10183453</td>
<td>c.-75_-55delGCACGCAGCTCCGCCCGCGCGC</td>
<td>NM_000551.3</td>
<td>rs727503744</td>
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<td></td>
</tr>
</tbody>
</table>

### Test performance

Blueprint Genetics offers a comprehensive Hereditary Paraganglioma-Pheochromocytoma Panel that covers classical genes associated with Carney-Stratakis syndrome, hereditary paraganglioma-pheochromocytoma, multiple endocrine neoplasia type 2, neurofibromatosis type 1 and Von Hippel-Lindau disease. 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 Hereditary Paraganglioma-Pheochromocytoma Panel

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
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</thead>
<tbody>
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</tbody>
</table>

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

- Adrenaltumors.org
- American Multiple Endocrine Neoplasia Support
- Child Neurology Foundation - NF Type 1
- VHL Alliance
- NORD - Pheochromocytoma
- NORD - Multiple Endocrine Neoplasia Type 2
- NORD - Neurofibromatosis Type 1 (NF1)
- NORD - Von Hippel-Lindau Syndrome
- Gene Reviews - Hereditary Paraganglioma-Pheochromocytoma Syndromes
- Gene Reviews - Multiple Endocrine Neoplasia Type 2
- Gene Reviews - Neurofibromatosis 1
- Gene Reviews - Von Hippel-Lindau Syndrome