Flecked Retina Disorders Panel

Test code: OP1401

The Blueprint Genetics Flecked Retina Disorders Panel is a 11 gene test for genetic diagnostics of patients with clinical suspicion of flecked retina disorder.

The panel covers genes associated with different flecked retina disorders, such as fundus albipunctatus, fundus flavimaculatus (Stargardt disease) and Bietti crystalline dystrophy. Differential diagnosis include choroideremia and X-linked retinoschisis. The panel is included in the Retinal Dystrophy Panel.

About Flecked Retina Disorders

Flecked retina disorders are a group of conditions characterized by multiple yellow-white retinal lesions of various size and configuration, without vascular or optic nerve abnormalities. Flecked retina disorders may be stationary or progressive and range from benign to visually devastating. Fundus albipunctatus show autosomal recessive inheritance and is mainly caused by mutations in the RDH5 gene. Stargardt disease or fundus flavimaculatus is a progressive form of juvenile macular degeneration with considerable clinical and genetic heterogeneity. Inheritance pattern can be either autosomal dominant or recessive. Stardardt disease is caused by mutations in ABCA4, PROM1 or ELOVL4. Bietti crystalline dystrophy is inherited in an autosomal recessive manner and is caused by mutations in CYP4V2.

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 Flecked Retina Disorders 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>ABCA4</td>
<td>Stargardt disease, Retinitis pigmentosa, Cone rod dystrophy, Retinal dystrophy, early-onset severe, Fundus flavimaculatus</td>
<td>AR</td>
<td>203</td>
<td>1012</td>
</tr>
<tr>
<td>CHM</td>
<td>Chorioideremia</td>
<td>XL</td>
<td>26</td>
<td>268</td>
</tr>
<tr>
<td>CYP4V2</td>
<td>Retinitis pigmentosa, Bietti crystalline corneoretinal dystrophy</td>
<td>AR</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>ELOVL4</td>
<td>Stargardt disease, Ichthyosis, spastic quadriplegia, and mental retardation, Spinocerebellar ataxia</td>
<td>AD/AR</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>PROM1</td>
<td>Stargardt disease, Retinitis pigmentosa, Cone rod dystrophy, Macular dystrophy, retinal,</td>
<td>AD/AR</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>PRPH2</td>
<td>Chorioidal dystrophy, central areolar, Macular dystrophy, vitelliform, Retinitis pigmentosa, Retinitis punctata albscens, Macula dystrophy, patterned</td>
<td>AD/Digenic</td>
<td>28</td>
<td>157</td>
</tr>
<tr>
<td>RDH5</td>
<td>Fundus albipunctatus</td>
<td>AR</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>RHO</td>
<td>Retinitis pigmentosa, Night blindness, congenital stationary, Retinitis punctata albscens</td>
<td>AD/AR</td>
<td>50</td>
<td>197</td>
</tr>
<tr>
<td>RLBP1</td>
<td>Newfoundland rod-cone dystrophy, Fundus albipunctatus, Bothnia retinal dystrophy, Retinitis punctata albscens</td>
<td>AR</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>RS1</td>
<td>Retinoschisis</td>
<td>XL</td>
<td>24</td>
<td>235</td>
</tr>
<tr>
<td>VPS13B</td>
<td>Cohen syndrome</td>
<td>AR</td>
<td>128</td>
<td>184</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/); 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>ABCA4</td>
<td>Chr1:94576926</td>
<td>c.302+68C&gt;T</td>
<td>NM_000350.2</td>
<td>rs761188244</td>
</tr>
<tr>
<td>ABCA4</td>
<td>Chr1:94493073</td>
<td>c.4539+1928C&gt;T</td>
<td>NM_000350.2</td>
<td></td>
</tr>
<tr>
<td>ABCA4</td>
<td>Chr1:94493000</td>
<td>c.4539+2001G&gt;A</td>
<td>NM_000350.2</td>
<td></td>
</tr>
<tr>
<td>ABCA4</td>
<td>Chr1:94492973</td>
<td>c.4539+2028C&gt;T</td>
<td>NM_000350.2</td>
<td>rs869320785</td>
</tr>
<tr>
<td>ABCA4</td>
<td>Chr1:94484082</td>
<td>c.5196+1056A&gt;G</td>
<td>NM_000350.2</td>
<td></td>
</tr>
<tr>
<td>ABCA4</td>
<td>Chr1:94484001</td>
<td>c.5196+1137G&gt;A</td>
<td>NM_000350.2</td>
<td>rs778234759</td>
</tr>
<tr>
<td>ABCA4</td>
<td>Chr1:94484001</td>
<td>c.5196+1137G&gt;T</td>
<td>NM_000350.2</td>
<td></td>
</tr>
<tr>
<td>PROM1</td>
<td>Chr4:15989860</td>
<td>c.2077-521A&gt;G</td>
<td>NM_0006017.2</td>
<td>rs796051882</td>
</tr>
</tbody>
</table>

Test performance

Blueprint Genetics offers a comprehensive Flecked Retina Disorders Panel that covers classical genes associated with Bietti crystalline dystrophy, choroideremia, Cohen syndrome, flecked retina disorder, fundus albipunctatus, retinitis punctata albescens, Stargardt disease and x-linked retinoschisis. 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
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.

Reference information

Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations - 2016

CPT codes

SEQ ☑ 81479
DEL/DUP ☑ 81479
ICD codes

Commonly used ICD-10 codes when ordering the Flecked Retina Disorders Panel

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>H35.9</td>
<td>Flecked retina disorder</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

- Fighting Blindness
- Foundation Fighting Blindness
- Retina International
- Royal National Institute of Blind People
- Choroideremia Research Foundation
- Retina Australia
- Cohen syndrome Association
- NORD - Choroideremia
- NORD - Retinoschisis
- NORD - Cohen Syndrome
- Gene Reviews - Choroideremia
- Gene Reviews - Retinoschisis
- Gene Reviews - Cohen syndrome
- Gene Reviews - Bietti Crystalline Dystrophy