Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome (BHDS), caused by heterozygous germline pathogenic variants in the *FLCN* gene, is commonly characterized by cutaneous manifestations, pulmonary cysts (typically with history of pneumothorax), and various renal tumors.

**Disease Overview**

**Common Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>% of Patients</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous manifestations</td>
<td>84.1,2</td>
<td>Cutaneous manifestations are unusual in individuals age &lt;20 yrs</td>
</tr>
<tr>
<td>Pulmonary cysts</td>
<td>70-85.3</td>
<td>The age when cysts start to appear is unknown; childhood onset is likely</td>
</tr>
<tr>
<td>Spontaneous recurrent pneumothorax</td>
<td>Approximately 25.4</td>
<td>–</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>19-35.4,5,6,7</td>
<td>Frequency of specific tumor types:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chromophobe: 19/49 individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clear cell: 15/49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hybrid oncocytic: 5/49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Papillary: 4/49</td>
</tr>
</tbody>
</table>

*Frequency of chromophobe or hybrid renal cell carcinoma was higher in studies that focused on renal symptoms. Sources: Toro, 2008; Schmidt, 2015; Kunogi, 2010; Houweling, 2011; Zbar, 2002; Sattler, 2018; Johannesma, 2019.

**Clinical Criteria**

BHDS should be suspected in individuals with any of the following major or minor criteria. The diagnosis of BHDS is established in an individual with one major or two minor criteria.

- **Major criteria**
  - Five or more fibrofolliculomas/trichodiscomas with at least one confirmed histologically
  - A single pathogenic *FLCN* germline variant
- **Minor criteria**
  - Multiple lung cysts, with or without spontaneous primary pneumothoraces
  - Early-onset renal cancer (<50 years of age)
  - Multifocal or bilateral renal cancer
  - Renal cancer of mixed chromophobe and oncocytic histology
  - First-degree relative with BHDS

**Genetics**

**Gene**

*FLCN* (NM_144997)
Etiology

Approximately two individuals per million in the general population are estimated to have BHDS. Over 400 families affected by BHDS have been reported.

Inheritance

Autosomal dominant

Penetrance

High; approximately 90-95% of individuals with a single pathogenic FLCN variant will develop at least one feature of BHDS.

Recurrent Variants

Twenty to 24% of families with BHDS were found to have either the pathogenic variant c.1285delC or c.1285dupC, located in the polycytosine mutational hotspot in exon 11.

Test Interpretation

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low with methodology used for germline assays
- Individuals with hematologic malignancy and/or a previous allogeneic bone marrow transplantation should not undergo molecular genetic testing on a peripheral blood specimen.
  - Testing of cultured fibroblasts is required for accurate interpretation of test results.
- When a relative has a previously identified pathogenic variant, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS, also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Sensitivity and Specificity

Clinical Sensitivity

Approximately 96%

Analytic Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate (%) and 95% Credibility Region</th>
<th>Analytic Specificity (NPA) Estimate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99 (96.9-99.4)</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

*PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

* Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

* In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants
<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytic Sensitivity (PPA) Estimate(^a) (%) and 95% Credibility Region</th>
<th>Analytic Specificity (NPA) Estimate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletions 1-10 bp(^b)</td>
<td>93.8 (84.3-98.2)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Insertions 1-10 bp(^b)</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>
| Exon-level\(^c\) deletions | 97.8 (90.3-99.8) [2 exons or larger]  
62.5 (38.3-82.6) [single exon] | >99.9 |
| Exon-level\(^c\) duplications | 83.3 (56.4-96.4) [3 exons or larger] | >99.9 |

\(^a\) PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

\(^b\) Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

\(^c\) In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

### Results

<table>
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<tr>
<th>Result</th>
<th>Variant(s) Detected</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>One <strong>FLCN</strong> pathogenic variant detected</td>
<td>Consistent with a diagnosis of Birt-Hogg-Dubé syndrome</td>
</tr>
<tr>
<td>Negative</td>
<td>No pathogenic variants detected</td>
<td>Diagnosis of Birt-Hogg-Dubé syndrome is unlikely but not excluded</td>
</tr>
<tr>
<td>Uncertain</td>
<td><strong>FLCN</strong> variant(s) of uncertain clinical significance detected</td>
<td>Uncertain; it is unknown whether variant is benign or pathogenic</td>
</tr>
</tbody>
</table>

### Limitations

- A negative result does not exclude a diagnosis of BHDS or **FLCN**-associated tumors.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the **FLCN** gene
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes and/or repetitive or homologous regions

### References


Related Information

Hereditary Cancer Germline Genetic Testing
Hereditary Cancer Panel
Hereditary Renal Cancer Panel