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.

Featured ARUP Testing

Birt-Hogg-Dube Syndrome (FLCN) Sequencing and Deletion/Duplication 3005703

Method: Massively Parallel Sequencing

Recommended test to confirm a clinical diagnosis or family history of BHDS

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Common Features

Feature	% of Patients	Comment
Cutaneous manifestations (eg, fibrofolliculoma, acrochordons)	84[1,2]	Cutaneous manifestations are unusual in individuals age <20 yrs
Pulmonary cysts	70-85[3]	The age when cysts start to appear is unknown; childhood onset is likely
Spontaneous recurrent pneumothorax	Approximately 25[4]	—
Renal cell carcinoma	19-35[4,5,6,7]	Frequency of specific tumor types[a]: • Chromophobe:19/49 individuals • Clear cell: 15/49 • Hybrid oncocytic: 5/49 • Papillary: 4/49

[a]Frequency of chromophobe or hybrid renal cell carcinoma was higher in studies that focused on renal symptoms.

Sources: Toro, 2008[1]; Schmidt, 2015[2]; Kunogi, 2010[3]; Houweling, 2011[4]; Zbar, 2002[5]; Sattler, 2018[6]; Johannesma, 2019[7]

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.[8]

- 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 pneumothoraxes
  - 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.[9] Over 400 families affected by BHDS have been reported.[8]

Inheritance

Autosomal dominant

Penetrance

High; approximately 90-95% of individuals with a single pathogenic *FLCN* variant will develop at least one feature of BHDS.[8]

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.[6]

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%[8]

Analytic Sensitivity and Specificity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>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

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%)
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
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

Result	Variant(s) Detected	Clinical Significance
Positive	One *FLCN* pathogenic variant detected	Consistent with a diagnosis of Birt-Hogg-Dubé syndrome
Negative	No pathogenic variants detected	Diagnosis of Birt-Hogg-Dubé syndrome is unlikely but not excluded
Uncertain	*FLCN* variant(s) of uncertain clinical significance detected	Uncertain; it is unknown whether variant is benign or pathogenic

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

1. Toro JR, Wei MH, Glenn GM, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dubé syndrome: a new series of 50 families and a review of published reports. *J Med Genet*. 2008;45(6):321-331.

2. Kunogi M, Kurihara M, Ikegami TS, et al. Clinical and genetic spectrum of Birt-Hogg-Dube syndrome patients in whom pneumothorax and/or multiple lung cysts are the presenting feature. *J Med Genet*. 2010;47(4):281-2877.

3. Schmidt LS, Linehan WM. Molecular genetics and clinical features of Birt-Hogg-Dubé syndrome. *Nat Rev Urol*. 2015;12(10):558-569.

4. Houweling AC, Gijezen LM, Jonker MA, et al. Renal cancer and pneumothorax risk in Birt-Hogg-Dubé syndrome; an analysis of 115 FLCN mutation carriers from 35 BHD families. *Br J Cancer*. 2011;105(12):1912-1919.

5. Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. *Cancer Epidemiol Biomarkers Prev*. 2002;11(4):393-400.

6. Sattler EC, Reithmair M, Steinlein OK. Kidney cancer characteristics and genotype-phenotype-correlations in Birt-Hogg-Dubé syndrome. *PLoS One*. 20186;13(12):e0209504.

7. Johannesma PC, van de Beek I, van der Wel TJWT, et al. Renal imaging in 199 Dutch patients with Birt-Hogg-Dubé syndrome: Screening compliance and outcome. *PLoS One*. 2019;14(3):e0212952.

8. Sattler EC, Steinlein OK. Birt-Hogg-Dubé syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Jan 2020; Accessed: Aug 2022]

9. Muller ME, Daccord C, Taffé P, et al. Prevalence of Birt-Hogg-Dubé syndrome determined through epidemiological data on spontaneous pneumothorax and Bayes theorem. *Front Med (Lausanne)*. 2021;8:631168.

Related Information

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

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review September 2022 | Last Update June 2023