

Birt-Hogg-Dube Syndrome: *FLCN* Gene Sequencing

Test Code: VJ

Turnaround time: 6 weeks

CPT Codes: 81479 x1

Condition Description

Birt-Hogg-Dube syndrome (BHDS) is an autosomal dominant condition, the symptoms of which include hair follicle hamartomas, kidney tumors, and spontaneous pneumothorax. Individuals with BHDS usually present with multiple, small, skin-colored, dome-shaped papules distributed over the face, neck, and upper trunk. These cutaneous manifestations include fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas, and acrochordons; only fibrofolliculomas, however, are specific for BHDS. Skin lesions typically first appear in early adulthood and increase in size and number with age. Renal tumors are typically bilateral, multifocal, and usually slow growing; median age of tumor diagnosis is 48 years. The most common renal tumors are renal hybrids of oncocytoma and chromophobe histologic cell types. Lung cysts are mostly bilateral and multifocal; most individuals are asymptomatic but have a high risk for spontaneous pneumothorax. Some families have renal tumor and/or autosomal dominant spontaneous pneumothorax without cutaneous manifestations. Disease severity can vary significantly even within the same family.

The *FLCN* gene (17p11.2) (also known as *BHD*) is the only gene known to be associated with BHDS. Sequence analysis detects mutations in *FLCN* in 88% of affected individuals; therefore, some affected individuals who fulfill clinical diagnostic criteria do not have an identifiable mutation. Molecular genetic testing is indicated in all individuals known to have or suspected of having BHDS, including individuals with one of the following:

- o Five or more facial or truncal papules with at least one histologically confirmed fibrofolliculoma, with or without a family history of BHDS
- o Facial papules histologically confirmed to be angiofibroma in an individual who does not fit the clinical criteria of tuberous sclerosis complex (TSC) or multiple endocrine neoplasia type 1 (MEN1)
- o Multiple and bilateral chromophobe, oncocytic, and/or hybrid renal tumors
- o A single oncocytic, chromophobe, or oncocytic hybrid renal tumor and a family history of renal cancer with any of the above renal cell tumor types
- o A family history of autosomal dominant primary spontaneous pneumothorax without a history of smoking or COPD

The proportion of cases caused by *de novo* mutations is unknown because a sufficient number of parents have not been evaluated for subtle manifestation, nor are there sufficient data on clinically unaffected parents who have been evaluated by molecular genetic testing. Although some individuals diagnosed with BHDS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

For patients with suspected BHDS, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

[Click here](#) for the GeneTests summary on this condition.

Genes

[FLCN](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Birt-Hogg-Dube syndrome
- Individuals at-risk for Birt-Hogg-Dube syndrome due to family history

Methodology

PCR amplification of 14 exons contained in the *FLCN* gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

Detection

Clinical Sensitivity: 88%. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

Type: Whole Blood (EDTA)**Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: DNA, Isolated**Specimen Requirements:**

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Deletion/duplication analysis of the *FLCN* gene by CGH array is available for those individuals in whom sequence analysis is negative (VK).
- [Custom diagnostic mutation analysis \(KM\)](#) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.