FLCN (*BHD*) Gene Analysis in Birt-Hogg-Dubé Syndrome and Primary Spontaneous Pneumothorax

Disorder Also Known As: BHD; Fibrofolliculomas with trichodiscomas and acrochordons; PSP; Collapsed lung

Clinical Features:
Birt-Hogg-Dubé (BHD) syndrome is a rare inherited disorder characterized by small, firm, dome-shaped papules (fibrofolliculomas) distributed over the forehead, face, neck and upper trunk. Other associated skin lesions include trichodiscomas and acrocordons. Frequently observed non-dermatologic findings include spontaneous pneumothorax, lung cysts, and renal neoplasia. Some less common clinical features include parotid oncocytoma, multiple lipomas and angiolipomas, intestinal polyposis, neural tissue tumors, parathyroid adenomas, and large connective tissue nevi. Rarely, characteristic lesions have been found in the oral mucosa.

The renal tumors associated with BHD tend to be slow-growing lesions, with many patients developing bilateral and multifocal tumors over their lifetime. Most studies have found a median age at first renal tumor diagnosis to be in the individual's mid- to late-40s.[1,2] Reported risk for renal tumors varies (6.5%-41%).[3] The most common renal tumor histology seen in individuals with BHD is a hybrid chromophobe/oncocytic carcinoma, with chromophobe renal cell carcinomas (RCC) and benign oncocytic tumors also prevalent.

Primary spontaneous pneumothorax (PSP), or collapsed lung, results from the presence of air in the pleural space in the absence of a precipitating event such as trauma or lung disease. Approximately 89% of individuals with BHD have multiple, bilateral lung cysts and 24% report a history of at least one pneumothorax.[4] Affected individuals have subpleural blebs or bullae in the lungs (localized emphysema-like changes) that are associated with destruction of lung tissue. The majority of cases are sporadic. Isolated familial PSP is rarer, and has been associated with variants in the *FLCN* gene in a small number of families.

Inheritance Pattern:
Birt-Hogg-Dubé Syndrome is inherited in an autosomal dominant manner; *de novo* (new) cases have been reported.

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *FLCN* are PCR amplified and capillary sequencing is performed. Bi directional sequence is

assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of *FLCN* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of Birt-Hogg-Dubé Syndrome as outlined above. Sequence analysis is expected to identify pathogenic variants in 84-88% of individuals with BHD.[1,3] In addition, large deletions and duplications in *FLCN* have been reported in individuals affected with BHD.[5]

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

References:

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