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 genodermatosis 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 (30-50 fold increased risk over the general population), lung cysts, and renal neoplasia (7-9 fold increase risk). 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 average age at presentation is 25-years.

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. 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/Genetics:
Autosomal dominant with variable expressivity; approx. 15% of cases are de novo

Test Methods:
Analysis is performed by bi-directional sequencing of the coding regions and splice sites of exons 4-14 of the FLCN gene. If no variant is found by sequence analysis, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:

Germline variants in the FLCN gene have been found in 84% of patients with clinically-diagnosed BHD.[1] The sequencing approach used by GeneDx is expected to identify >95% of existing small intragenic variants, including the common cytosine duplication or deletion in exon 11 (see discussion in next section). The sensitivity of FLCN gene analysis in patients with isolated familial PSP is not defined due to the small number of published cases.

References:

1. Schmidt, L. et al., (2005) Am J Hum Genet. 76: 39-44.
2. Painter, J. et al., (2005) Am J Hum Genet. 76: 522-27.
3. Graham, R. et al., (2005) Am J Respir Crit Care Med. 172: 39-44.
4. Kunogi, M. et al., (2010) J Med Genet 47:281-287.