Birt-Hogg-Dubé Syndrome (BHD)

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Identity

Note: Birt-Hogg-Dubé syndrome (BHDS) is characterized by renal oncocytic tumors, benign skin tumors (fibrofolliculomas and trichodiscomas), and spontaneous pneumothorax. The first description of an affected family was provided by Birt, Hogg, and Dubé in 1977.

Inheritance: Autosomal Dominant with variable expressivity. Prevalence is estimated at about 1/200,000.

Clinics

Phenotype and clinics

BHDs is a genodermatosis characterized by the triad of benign tumors of the hair follicle, spontaneous pneumothorax and kidney tumors. These manifestations do not have to be simultaneously present in the same individual in order to establish a diagnosis of BHDS, since the phenotype is variable and penetrance is not complete. Patients may also suffer from colonic polyps and colorectal cancer. Cutaneous tumors are fibrofolliculomas, trichodiscomas and/or acrochordons. Fibrofolliculomas and trichodiscomas tend to appear in the third or fourth decade of life as small white or skin-colored multiple papules on the face, neck and upper trunk. Acrochordon is a non specific designation for small and soft skin tags. Multiple angiofibromas, lipomas and collagenomas have also been reported. Affected individuals have a high chance of developing cysts in the lungs and spontaneous pneumothorax. Although almost all patients who have BHDS have lung blebs (90%), but only a fifth will have spontaneous pneumothorax. The strong association of spontaneous pneumothorax with BHDS suggests that the presence of spontaneous pneumothorax in a member of a BHDS family could be used as a criterion for the diagnosis of BHDS.

Neoplastic risk

Approximately 27% of BHDS patients develop renal tumors of different histological type:
- chromophobe (34%),
- hybrid chromophobe/oncocytic (50%),
- oncocytoma (5%), and
- clear cell renal carcinoma (9%).

Hybrid tumors are most characteristic of this condition, and several lesions initially diagnosed as oncocytomas or chromofobe tumors have been defined as hybrid tumors upon reappraisal. Multiple histological types of kidney tumors can be found in the same BHDS family, in the same patient or even in the same kidney. Although colonic tumors have been observed in some families, it is not clear whether they represent a manifestation of BHDS.

Treatment

No specific medical treatment exists for the cutaneous lesions of BHDS. Surgical removal has provided definitive treatment of solitary perifollicular fibromas and electrodessication may be helpful in removal of multiple lesions, but these can recur. High-resolution CT scan is required in order to identify lung cysts.

Individuals at risk or affected by BHDS should be radiographically screened for renal tumors at periodic intervals and they are best treated with nephron sparing surgical approaches. Colonoscopy should be considered.
**Prognosis**
Prognosis depends on the number, type and age at diagnosis of kidney tumors. Hybrid and chromophobe tumors have malignant potential, while pure renal oncocytomas are benign. Mean age at diagnosis of kidney tumors is 50.7 years.

**Genes involved and Proteins**

**FLCN**

**Location:** 17p11.2

**DNA/RNA**
Description: Total gene size: 24971 bp.
Transcription: The protein contains a conserved SLS potential phosphorylation site, a glutamic acid-rich coiled-coil domain, an N-glycosylation site, and 3 myristoylation sites. Its function is yet unknown.

**Mutations**
Cytosine insertions or deletions in a mononucleotide repeat tract containing 8 cytosines within exon 11 are the most frequent constitutional mutations found, being detected in approximately 50% of BHDS families. These mutations result in an abnormally small, non functional folliculin protein. Other mutations located elsewhere in the coding sequence are heterogeneous. Overall, point mutations in the FLCN gene are found in approximately 80% of BHDS cases.

**References**


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