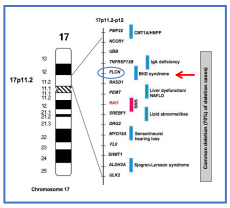
Smith-Magenis syndrome (SMS) & *Birt-Hogg-Dubé Syndrome (BHDS)*

Within the past 5 years there has been growing concern about the link between Smith-Magenis syndrome (SMS) and Birt-Hogg-Dubé (BHDS) leading to surveillance recommendations in adulthood. Published cases of renal cancer in adults with SMS[1] has expanded management recommendations to include kidney cancer surveillance starting at 20 years of age and evaluation for both skin and lung manifestations of BHDS as outlined in the table below. If an adult with SMS is diagnosed with BHD, the usual guidelines for BHDS monitoring should be considered, including regular abdominal imaging using MRI for early detection of cancer.

1. Reference: Vocke CD, Fleming LR, Piskorski AM, Amin A, Phornphutkul C, de la Monte S, Vilboux T, Duncan F, Pellegrino J, Braddock B, Middelton LA, Schmidt LS, Merino MJ, Cowen EW, Introne WJ, Linehan WM, Smith ACM. A diagnosis of Birt-Hogg-Dubé syndrome in individuals with Smith-Magenis syndrome: Recommendation for cancer screening. Am J Med Genet A. 2023 Feb;191(2):490-497. doi: 10.1002/ajmg.a.63049. Epub 2022 Dec 13. PMID: 36513625; PMCID: PMC10117402.

More information can be found on PRISMS website: https://www.prisms.org/birt-hogg-dube-and-smith-magenis-syndromes-separate-disorders-linked-through-17p11-2/

SMS & Birt-Hogg-Dubé (BHD) Syndrome?



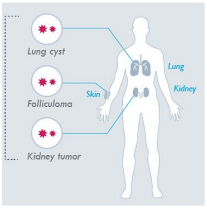
Birt-Hogg-Dubé (BHD) Syndrome

- Autosomal dominant syndrome
- Adult onset (4-5th decade)
- Caused by germline mutation of folliculin (FLCN) gene
- FLCN maps to chromosome 17p11.2 (within common SMS deletion)

Clinical features of BHD

- Skin papules-benign tumors/growths of the hair follicle (*fibrofolliculomas)* after puberty, most common manifestation
- Lung cysts, adult onset, multiple; normal lung function
- Risk of spontaneous pneumothorax, develops in 30% of those affected with BHD, average age 38 yrs.
- Renal cysts and slow growing renal tumors/cancer
  - Kidney cancer, develops in 12-34% of those affected with BHD, average age 49 yrs; requires mutation or deletion of 2nd copy of *FLCN* gene

What are the risks of developing BHD manifestations for individuals with SMS?



Source: www. PRISMS.org

- Individuals with SMS and chr17p11.2 deletion have 1 copy of *FLCN* gene (✱= del; one hit)
- Loss or mutation of remaining copy of *FLCN* gene can occur spontaneously and increase risk for developing kidney cancer. (✱= 2nd hit)
- If 2nd copy is lost there is a 7-fold increased risk for kidney cancer.
- As of 2022: 4 published cases of SMS & kidney cancer (all > 40 years); 2 of 4 with confirmed *FLCN* 2nd hit mutation.
- Individuals with *RAI1* mutations (10%) or uncommon deletions that do not encompass *FLCN* have same risk for kidney cancer as general population

Most people with SMS have an increased *chance* of developing BHD, but the diagnosis should never be made in children or adults who show no evidence of features. Having one hit (an SMS deletion) does not mean that a person has or ever will develop the clinical features of BHD.

PRISMS Reference LINK: https://www.prisms.org/birt-hogg-dube-and-smith-magenis-syndromes-separate-disorders-linked-through-17p11-2/

Recommended surveillance and screening for BHD manifestations begins in adulthood (age 20 and over)[1]

- SKIN: Dermatologic exam after puberty; biopsy to confirm fibrofolliculoma

- LUNG: High resolution chest computed tomography (CT) to detect lung cysts in adulthood to establish baseline; repeat imaging not necessary

- KIDNEY:
  - Risk for kidney cancer (2nd hit mutation *FLCN*) estimated at ~ 12-34% (Schmidt & Linehan, 2015)

Screening recommendations for Adults with SMS age 20y and older[1]

- Baseline abdominal imaging (MRI with contrast) to assess for renal (kidney) tumors.
- Repeat screening every 3 years thereafter

[1]Since BHD is considered an **adult-onset** disorder, we do not recommend any additional screening for symptoms related to BHD in **children** with SMS.

Birt-Hogg-Dubé syndrome (BHDS) is an autosomal dominant adult-onset medical condition characterized by symptoms involving the skin, lungs, and kidneys as summarized in the table below. Published cases of renal cancer in adults with SMS[1] has expanded management recommendations to include kidney cancer surveillance starting at 20 years of age and evaluation for both skin and lung manifestations of BHDS as outlined below. *Since BHD is considered an adult-onset disorder, we do not recommend any additional screening for symptoms related to BHD in children with SMS.*

	Birt-Hogg-Dubé syndrome (BHDS)	Surveillance Recommendations in SMS Adulthood (Ages 20yr and older)[1,2]
Skin	Skin papules-benign tumors/growths of the hair follicle (fibrofolliculomas) after puberty, most common manifestation	Dermatologic exam after puberty; biopsy to confirm fibrofolliculoma.
Lung	Lung cysts, adult onset, multiple; normal lung function. Risk of spontaneous pneumothorax, develops in 30% of those affected with BHDS, average age 38 yrs.	High resolution chest computed tomography (CT) to detect lung cysts in adulthood to establish baseline; repeat imaging not necessary.
Kidney	Renal cysts and slow growing renal tumors/cancer. Kidney cancer develops in 12-34% of those affected with BHDS, average age 49 years; requires mutation or deletion of 2nd copy of *FLCN* gene.	***Screening recommendations for adults with SMS age 20y and older:*** • Baseline abdominal imaging (MRI with contrast) to assess for renal (kidney) tumors. • Repeat screening every 3 years thereafter.

1 Vockie et al, 2023: A diagnosis of Birt-Hogg-Dubé syndrome in individuals with Smith-Magenis syndrome: Recommendation for cancer screening. Am J Med Genet A. 2023 Feb;191(2):490-497. PMID: 36513625; PMCID: PMC10117402.

[2] More information can be found on PRISMS website: https://www.prisms.org/birt-hogg-dube-and-smith-magenis-syndromes-separate-disorders-linked-through-17p11-2/