# Renal mass manifestations of the Birt-Hoge-Dube syndrome in a large clinical cohort

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## INTRODUCTION

**Birt-Hoge-Dube (BHD) Syndrome:**

- Underdiagnosed autosomal dominant condition
- Due to mutations in the folliculin (FLCN) gene
- Phenotypes: renal masses, lung cysts, spontaneous pneumothorax, fibrofolliculomas/trichodiscomas

**BHD Renal Masses:**

- Reportedly small masses with indolent course
- Most common pathology:
  - Chromophobe RCC (chRCC)
  - Oncocytoma
  - Hybrid oncocytic tumor

**Objective:** Report our center's experience with renal masses in BHD to expand the literature

## MATERIALS and METHODS

- Retrospective single center study
- BHD patient identification:
  - Clinical care
  - Penn Medicine BioBank
- Electronic medical record review of BHD patients with at least one renal mass:
  - Imaging indication/modality at diagnosis
  - Age at diagnosis
  - Number of lifetime tumors
  - Size of tumors
  - Tumor growth rate
  - Tumor pathology
  - Interventions on tumors
- Germline genetic testing of most patients
- Statistical Analysis:
  - Quantitative Variables: median and inter-quartile range (IQR)
  - Qualitative Variables: number and percentage of cohort

## RESULTS

**Table 1.** Renal tumors and treatments of the BHD Cohort.

| Variables | BHD Cohort (n = 81) |
|---|---|
| **Patient Characteristics [Median [IQR]]** | |
| Age at BHD Diagnosis [years] | 38 [28-57] |
| Patients with Known Renal Mass [N [%]] | 10 [12.3%] |
| Age at First Tumor Diagnosis [years] | 58 [50.8-60.2] |
| Number of Lesions [N [%]] | 1 [1-5] |
| Size of Tumor at Diagnosis [cm] | 1.5 [1-2.1] |
| Range of Tumor Size at Diagnosis [cm] | 0.8-12 |
| **Diagnosis of First Tumor [N [%]] (n = 10)** | |
| **Imaging Modality** | |
| MRI | 8 [80%] |
| CT | 1 [10%] |
| PET/CT | 1 [10%] |
| **Indication for Imaging** | |
| Abdominal Pain | 3 [30%] |
| Flank Pain | 1 [10%] |
| Abnormal Liver Function Tests | 1 [10%] |
| Imaging for Non-Renal Malignancy | 3 [30%] |
| Surveillance of Known BHD | 2 [20%] |
| **Treatment by Patient [N [%]] (n = 10)** | |
| None/Surveillance | 6 [60%] |
| Partial Nephrectomy | 2 [20%] |
| Bilateral Partial Nephrectomies | 1 [10%] |
| Radical Nephrectomy | 1 [10%] |
| **Treatment by Tumor [N [%]] (n = 15)** | |
| None/Surveillance | 10 [66.7%] |
| Partial Nephrectomy | 4 [26.7%] |
| Radical Nephrectomy | 1 [6.7%] |
| **Pathology [N [%]] (n = 15)** | |
| Unknown/Surveillance | 9 [60%] |
| Chromophobe RCC | 3 [20%] |
| Clear Cell RCC | 1 [6.7%] |
| Papillary RCC | 1 [6.7%] |
| Angiomyolipoma [MRI diagnosis] | 1 [6.7%] |
| **Growth of Surveilled Tumors [Median [IQR]] (n = 9)** | |
| Interval of Follow Up [years] | 2.3 [2.3-5.6] |
| Growth Rate [cm/yr] | 0 [-0.02 - 0] |
| Range of Growth Rate [cm/yr] | -0.04 - 0.43 |
| **Germline Mutations in Patients with Renal Mass† [N] (n = 9)** | |
| Partial deletion including exon 1 | 2* |
| c.1474_1475delAAinsG | 1 |
| c.1219delA | 1 |
| c.1021delC | 1 |
| c.927_954dup28 | 1 |
| c.1062+T>C | 1 |
| c.1285dupC | 1** |
| c.1117C>T | 1 |

† One patient requiring partial nephrectomy did not have germline genetic testing.
* Both patients required surgical intervention [one radical nephrectomy, one bilateral partial nephrectomy].
** Required partial nephrectomy.

## LIMITATIONS

- Retrospective study
- Despite large overall BHD cohort, small sample of patients with renal masses
- Limited histologic diagnosis of renal masses
- Limited length of follow up imaging of surveilled tumors

## CONCLUSIONS

- 12.3% of the BHD cohort developed renal tumors, consistent with prior reports
- Age at tumor onset was older than other hereditary renal cancer syndromes
- BHD-associated tumors were small and indolent with static growth rate
- chRCC was the most common histology although papillary and clear cell RCC were also seen
- Germline genetic mutation status may provide an opportunity for precision medicine in these patients

## FUTURE DIRECTIONS

- Further explore the functional impacts of the identified germline mutations in BHD patients with renal tumors
- Continue surveillance of BHD-associated renal masses over a longer follow up period

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