A Lynch-Like Presentation of Birt-Hogg-Dube Syndrome (BHDS)

Carolyn Rogers, Austin Klein, Kallyn Stumm, Cristina Nixon, Rachael Brandt*, Jamie Mushlin, Michael Dabrow and Terri McHugh

Main Line Health, Lankenau Institute for Medical Research, Thomas Jefferson University, Pennsylvania, USA

Abstract

Introduction

Over the past few years, next generation sequencing technology and the use of panel genetic testing has quickly replaced traditional single gene testing using Sanger sequencing. While gene panels are capable of testing for multiple genetic conditions simultaneously thereby decreasing overall costs, personal and family history still play an important role in determining an appropriate gene panel and without attention in laboratory and test selection, rare syndromes may be missed.

Case report

Multiple members from a family affected with Lynch-syndrome cancers and meeting Amsterdam II criteria presented nearly simultaneously for genetic testing based on personal history, family history and absent immunohistochemical staining in select tumors. Careful review of the pathology and of the family history, including benign findings, altered the initial test approach for the family. A pathogenic FLCN mutation, consistent with Birt-Hogg-Dube syndrome (BHDS) was identified in multiple family members.

Discussion

This case illustrates the utility of panel testing in comprehensive genetic evaluations. Due to the pre-test clinical suspicion of multiple cancer predisposition syndromes, this family was an excellent example of an ideal clinical scenario for panel testing. By submitting an expanded panel test for these family members, differential diagnoses were assessed simultaneously, and overall cost was lower. Findings significantly impacted the medical management guidelines for individuals identified to have BHDS.

*Corresponding author: Rachael Brandt, Main Line Health, Lankenau Institute for Medical Research, Thomas Jefferson University, Pennsylvania, USA. Tel: +1 4844768153; E-mail: KleinA@MLHS.ORG


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adenocarcinoma of the ascending colon with metastatic disease to the liver (Figure 1). IHC showed loss of MLH1 and PMS2. Additional personal cancer history included three metachronous bladder cancers between his 70s and 90s and a history of melanoma at age 86. He was a prior smoker (pack year history unknown). Further tumor analysis for BRAF V600E and/or hypermethylation or germline testing was unable to be completed prior to his unexpected death secondary to complications.

Several months later, individual II.4’s daughter, individual III.9 presented with a diagnosis of endometrioid adenocarcinoma at age 54. Immunohistochemical staining of the mismatch repair proteins was performed and showed loss of MSH6 protein staining. The MLH1, MSH2 and PMS2 protein staining was intact. Additional history included personal history of a right sided colon cancer with liver metastases at age 41 treated with an open right hemicolectomy with partial left hepatic resection for metastasis and adjuvant FOLFOX chemotherapy, currently without evidence of recurrence, a family history of renal cancer in her sister and of gastric cancer in her paternal grandfather.

Individual III.9 declined further genetic evaluation, however, her sister with renal cancer, individual III.4, elected to pursue this. She reported to the program a personal history of two tumors of the right kidney at age 59. Pathology was obtained and confirmed a chromophobe renal cell carcinoma in the middle pole (2.5 cm) and a multilocular cystic tumor, in the lower pole combined chromophobe and cystic clear cell carcinoma. An adrenal cortical adenoma was also noted on surgical specimen. Given the renal pathology and family history, a genetic panel was ordered that included MMR genes, FLCN and other genes associated with renal and/or colorectal/endometrial cancer. A pathogenic FLCN mutation, c.557G>A (p.Trp186*), and a variant of uncertain significance, c.3857G>A in POLE, were identified.

This mutation in FLCN truncates the protein prematurely at codon 186 and is classified as pathogenic in the ClinVar database (Variation ID: 230137). No reported mutations/variants were identified in any of the other genes analyzed by sequencing and/or deletion/duplication analysis: APC, ATM, AXIN2, BAP1, BARD1, BMP11, BRCA1, BRCA2, BRIPI, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, FH, GEM1, MEN1, MET, MLH1, MRE11A, MSH2, MSH6, MUT-YH, NBN, NF1, PALB2, PMS2, POLD1, PTEN, RAD50, RAD51C, RAD51D, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARC4, STK11, TP53, TSC1, TSC2, VHL or XRCC2. Subsequent evaluation of individual III.4’s medical records revealed acrochordons and a history of lung cysts. A history of fibrofolliculomas or colorectal polyposis was denied.

Upon identification of the FLCN mutation in the family, individual III.9 reconsidered genetic evaluation. Individual III.9 reported a history of bilateral axillary acrochordons (skin tags). A report from a CT scan of the chest, abdomen and pelvis from 4 years prior showed a stable pattern of scattered bilateral pulmonary bullae and blebs (cysts) and a stable subcentimeter left renal cortical hypodensity. A 43 gene hereditary cancer panel was ordered, which confirmed presence of the FLCN c.557G>A mutation. She tested negative for the POLE VUS and no mutations were identified in any of the Lynch syndrome genes, including MSH6, or other genes tested.

Additionally, individual III.4’s other sister, individual III.7, presented for testing. She reported a personal history of several skin lesions (nasal angiofibroma/fibrous papule, basal cell carcinoma of the left distal pretilia and intradermal nevus of the neck, verrucous keratosis and basal cell carcinoma of the left arm) and 3 colorectal polyposis, type unknown. Multi-gene panel testing was performed and the FLCN mutation was also identified (Table 1).

<table>
<thead>
<tr>
<th>Individual</th>
<th>Clinical Finding</th>
<th>Genetic Test Result</th>
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<tbody>
<tr>
<td>II.4</td>
<td>Colorectal cancer</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
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<td></td>
<td>Bladder x3</td>
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<tr>
<td>III.4</td>
<td>Chromophobe renal cell cancer</td>
<td>FLCN+</td>
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<tr>
<td></td>
<td>Acrochordons</td>
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<td></td>
<td>Lung cysts</td>
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<tr>
<td>III.7</td>
<td>Several skin lesions (nasal angiofibroma/fibrous papule, basal cell carcinoma and intradermal nevus of the neck, verrucous keratosis and basal cell carcinoma)</td>
<td>FLCN+</td>
</tr>
<tr>
<td></td>
<td>3 colorectal polyposis, type unknown</td>
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<tr>
<td>III.9</td>
<td>Endometrioid cancer</td>
<td>FLCN+</td>
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<td></td>
<td>Colorectal cancer</td>
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<td>Bilateral axillary acrochordons scattered bilateral pulmonary bullae and blebs (cysts)</td>
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<td>Stable subcentimeter left renal cortical hypodensity</td>
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Given family X’s presentation, additional testing of colorectal tumor DNA is under consideration in an effort to provide explanation of the absent IHC staining observed in family members affected with colorectal cancer. While lineage of the FLCN mutation has not yet been established, a paternal first cousin has been reported to have had multiple spontaneous pneumothoraces.

**Discussion**

Birt-Hogg-Dubé Syndrome (BHDS) is a rare cancer predisposition syndrome first described by three Canadian physicians in 1977 [11]. BHDS is inherited in an autosomal dominant manner and is caused by loss-of-function pathogenic mutations in the gene Folliculin (FLCN) [12]. Approximately 91-93% of individuals meeting clinical diagnostic criteria for BHDS will have an identifiable mutation in FLCN by sequencing or deletion/duplication analysis [13].
BHDS is primarily characterized by three features: benign cutaneous manifestations, pulmonary cysts and spontaneous pneumothorax and renal tumors. Affected individuals vary significantly in presentation and severity, even within families. Skin growths include fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas and acrochordons [14,15]. These typically appear when individuals are in their twenties or thirties and can increase in size and number over time. Lung cysts are mostly bilateral and multifocal and have been observed in up to 89% [16] of individuals with pathogenic FLNC mutations; most individuals are asymptomatic but have a high risk for spontaneous pneumothorax [17]. Reports for renal involvement vary, as 12% to 34% of individuals with BHDS develop renal (kidney) tumors [17,18], which also tend to be bilateral and multifocal and are usually slow growing; median age of renal tumor diagnosis is 48 years.

Additional findings of BHDS continue to be characterized. Since 2000, several affected individuals have been reported with parotid oncocytomas [19,20]. Other features such as thyroid cancer or nodules and oral papules have also been reported [14,21]. Early reports of BHDS included intestinal polyps and colorectal cancer as an associated feature of the condition [17,22].

Further studies concerning the BHDS clinical spectrum have failed to consistently establish colonic neoplasms as a clinical feature [23,24]. Recent work has suggested the possibility of genotype/phenotype correlations underlying the risk for colorectal findings in BHDS [25] with carriers of mutation FLNC c.1285dupC displaying a significantly higher risk for colorectal neoplasia compared to carriers of FLNC c.610delGCinsTA. Toro et al., [20] additionally reported occurrences of Squamous Cell Carcinoma (SCC) of the head, neck, and cervix, Hodgkin’s disease, uterine cancer, prostate cancer, breast cancer, rhabdomyoma and an adrenal mass in their study of 51 families with BHDS; none of these findings, however, have been confirmed to be part of the BHDS clinical spectrum to date.

Summary Points

Family X’s initial presentation, of gastric, colorectal and endometrial cancers met Amsterdam II criteria [26] for possible Lynch syndrome. This suspicion was furthered by the loss of MSH6 in III.9 endometrial cancer specimen. It was not until III.4 presented and renal pathology reports were obtained that the possibility of a familial FLNC mutation was raised. This serves to highlight the necessity of accurate and complete family histories when pursing genetic testing. Without this information, this family would not have met criteria for FLNC gene testing, and may not have been evaluated for this rare syndrome. Due to the pre-test clinical suspicion of multiple cancer predisposition syndromes, family X was an excellent example of an ideal clinical scenario for panel testing. By submitting panel testing for these patients, the main concerns on the differential diagnosis were assessed simultaneously, and overall cost was lower. Additionally, as the clinical associations of cancer syndromes remains under investigation, panel testing allows for further elucidation of germline mutation risks in families that may not have a traditional presentation. This type of report and case report is an opportunity to revisit the known phenotype of FLNC mutation carriers.

Had individual III.4 not presented for genetic evaluation and permitted release of her renal cancer pathology, the chromophobe renal cancers would not have been confirmed. This pathology directed the testing plan for the family; testing of FLNC would not have been considered based on III.9 personal or reported history at that time. Furthermore, she would not have met clinical testing criteria for Birt-Hogg-Dubé syndrome and depending on the lab used or panel ordered, FLNC may not have been included. In fact, many healthcare providers may have ordered only MSH6 testing given the abnormal IHC result in the endometrial tissue and not considered any further genes for evaluation. Not only can panel testing reveal unexpected genetic test results, it can be strategically used for a more thorough genetic evaluation or to test genes that may have not been able to be tested independently.

References


