INTERNAL MEDICINE

□ CASE REPORT □

Birt-Hogg-Dubé Syndrome with Clear Cell Renal Cell Carcinoma in a Chinese Family

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Abstract

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant genodermatosis that presents as a clinical triad including follicular hamartomas, renal neoplasms and lung cysts associated with an increased risk of pneumothorax. *FLCN* gene defects have been identified as being responsible for BHDS. We herein report the case of a 67-year-old woman with the full-blown BHDS phenotype, characterized by skin lesions, multiple lung bullae and renal neoplasms. In her family history, one of the patient's sons exhibited a similar phenotype, without renal neoplasms. Due to the relatively late age of onset of renal neoplasms among variable BHDS phenotypes, follow-up imaging is recommended for the son who has not yet developed renal neoplasms.

Key words: Birt-Hogg-Dubé syndrome, folliculin, lung bullae, pneumothorax, renal neoplasm

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Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant genodermatosis first reported by Birt, Hogg and Dubé in 1977 (1). It is characterized by a clinical triad including follicular hamartomas, pulmonary cysts and an increased risk of developing kidney tumors (2). The combination of these three phenotypic manifestations may vary among affected family members (3). As many as 85% of patients develop pulmonary cysts, with or without spontaneous pneumothorax, and the penetrance for skin lesions is approximately 80%. However, only 30% of BHDS patients develop renal neoplasms, the most threatening manifestation of this syndrome (4-6). A series of renal tumor types has been reported, including hybrid oncocytic/chromophoberenal tumors, chromophobe renal cell carcinoma, clear cell renal cell carcinoma and oncocytoma, at frequencies of 50%, 34%, 9% and 5%, respectively (7). Moreover, the development of clinical features appears to be age-related (8). Lung symptoms may occur as young as 7 years of age, whereas skin lesions usually develop in the patient's 20's or 30's (9). In contrast, the onset of BHDS-associated renal tumors primarily occurs after 40 years of age (2).

BHDS results from the presence of germline mutations in the *FLCN* gene on 17p11.2. Mutations have been found along the entire coding region of the *FLCN* gene, and duplication/deletion of cytosinein the polycytosine tract in exon 11 has recurrently been observed as a mutational hotspot (3). Moreover, most *FLCN* germline mutations are thought to produce truncated folliculin.

In this study, we report a Chinese family affected by BHDS in whom a germline mutation in the gene *FLCN* was detected on a mutation analysis.

Case Report

A two-generation Chinese family with three subjects, a mother and her two sons, was enrolled in a clinical study and *FLCN* germline mutation analysis. The index patient was a 67-year-old woman with multiple dome-shaped papules on the skin. An abdominal computed tomography (CT) scan showed bilateral, multiple circular and oval high-density masses predominating in the kidneys, and a further

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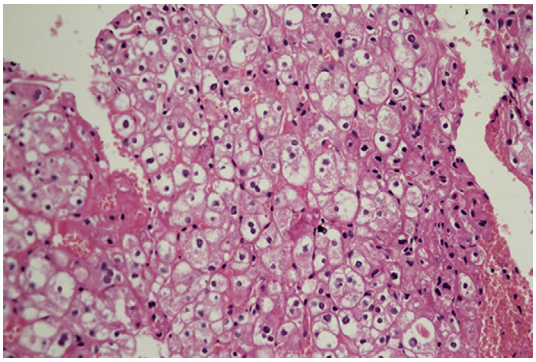

Figure 1. Microphotograph (Hematoxylin and Eosin staining) of granular cell type renal carcinoma in the index patient. Granular cell carcinoma of the kidney with polygonal cells: the cytoplasm stained red, and granular nuclei round or oval in shape were detected. Original magnification ×40.

Figure 3. Skin manifestations in the BHDS-affected son. Multiple dome-shaped papules on the neck.

evaluation of a surgical biopsy demonstrated the histologic features of clear cell renal cell carcinoma (Fig. 1). Imaging of the chest with CT disclosed multiple bilateral lung bullae (Fig. 2). Of the two other subjects, the 33-year-old younger son presented with multiple pale dome-shaped papules on his neck (Fig. 3), as well as cystic lung lesions with spontaneous pneumothorax documented on CT scans of the chest. The 40-year-old elder son was classified as BHDS-unaffected, as he showed no indications of BHDS-affected manifestations on a physical examination. Aside from the two BHDS-affected patients included in this report, the medical records of no other close relatives showed evidence of the typical BHDS phenotype or a history of cancer in this family.

Genetic testing was conducted after obtaining informed consent from three subjects. Sequencing of the *FLCN* gene covering the entire coding sequence and flanking intron region of 14 exons led to the identification of six variants in total. Among these variants, five were reported SNPs and observed in all three family members (Table). A heterozygous mutation c.1153 C>T in exon 10 was detected in the two BHDS subjects. However, the elder son, clinically considered to be BHDS-unaffected, showed wild-type alleles at this site, indicating that this mutation is segregated with the disease (Fig. 4). In addition, the mutation was predicted to create a premature stop at codon 385, resulting in a C-terminus truncated protein (Q385*).

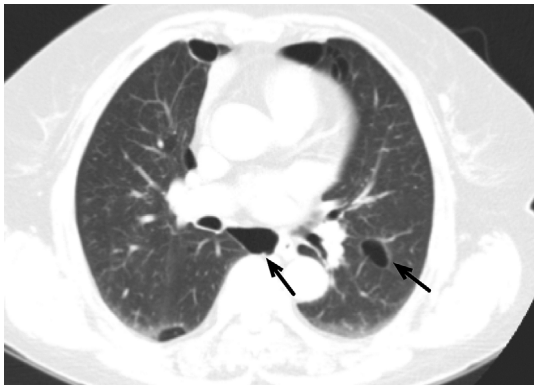

Figure 2. CT scan of the index patient's chest showing multiple bilateral thin-walled bullae; the largest two are indicated by arrows.

Discussion

Previous reports have shown that phenotypic manifestations are variably combined in BHDS-affected patients (3). As reported by Schmidt et al., up to 80% of patients with BHDS have skin lesions. Many researchers have indicated that lung cysts are the most common manifestations of BHDS, noted in more than 85% of patients (10, 11). It is believed that lung cysts increase the risk of pneumothorax due to rupture of a cyst on the surface of the lung. Approximately 24% of patients screened for lung cysts have a history of spontaneous pneumothorax, as investigated by Toro et al. (11). Compared to the other manifestations of BHDS, the occurrence of renal tumors is relatively low, likely between 12-34%, according to different studies (10). In spite of its relatively low prevalence, clinical diversity is observed in BHDS-associated renal tumors, primarily including hybrid oncocytic/chromophobe tumors (50%) and chromophobe renal cell carcinoma (34%) (7).

Recent evidence also suggests that the development of BHDS-associated features is age-related (8). For example, skin manifestations usually appear in individuals in their 20's and 30's (12). In addition, lung cysts carry a 50-fold higher risk for pneumothorax, and the results obtained by Toro et al. suggest that the median age of onset of pneumothorax is 38 years (11). In contrast, BHDS-associated renal tumors usually exhibit a relatively later onset. Zbar et al. studied 223 members of 33 BHDS families and demonstrated that the median age at diagnosis of renal cancer in the patient group was 51 years (2). Similar results have been reported by Schmidt et al. in a study of 187 BHDS-affected individuals (3).

Thus far, over 400 BHDS pedigrees have been reported. However, most cases involved Caucasians, with only two

Table. **Summary of 5 SNPs Identified in *FLCN* Gene by Sequencing**

dbSNP	Genomic position*	mRNA position†	Location or ΔAA†	Alleles†	Minor Allele	MAF in CHB
rs1736209	17,140,485	c.-487	5' UTR	G>C	G	0.17
rs1708629	17,140,297	c.-299	5' UTR	C>T	C	0.39
rs1736219	17,127,471	c.397-14	Intron 5	C>T	C	0.39
rs3744124	17,124,815	c.871+36	Intron 8‡	G>A	A	0.19
rs8065832	17,122,327	c.1062+6	Intron 9	C>T	C	0.35

ΔAA: change in amino acid
MAF: minor allele frequency
CHB: samples from Han Chinese in Beijing, China studied in Hapmap project
†Referenced to the positive strand and folliculin isoform 1 [GenBank:NM_144997]
*Referenced to chromosome 17 on the Human Feb. 2009 (hg19) assembly
‡p.Gly303Arg in isoform 2 [GenBank:NM_144606]

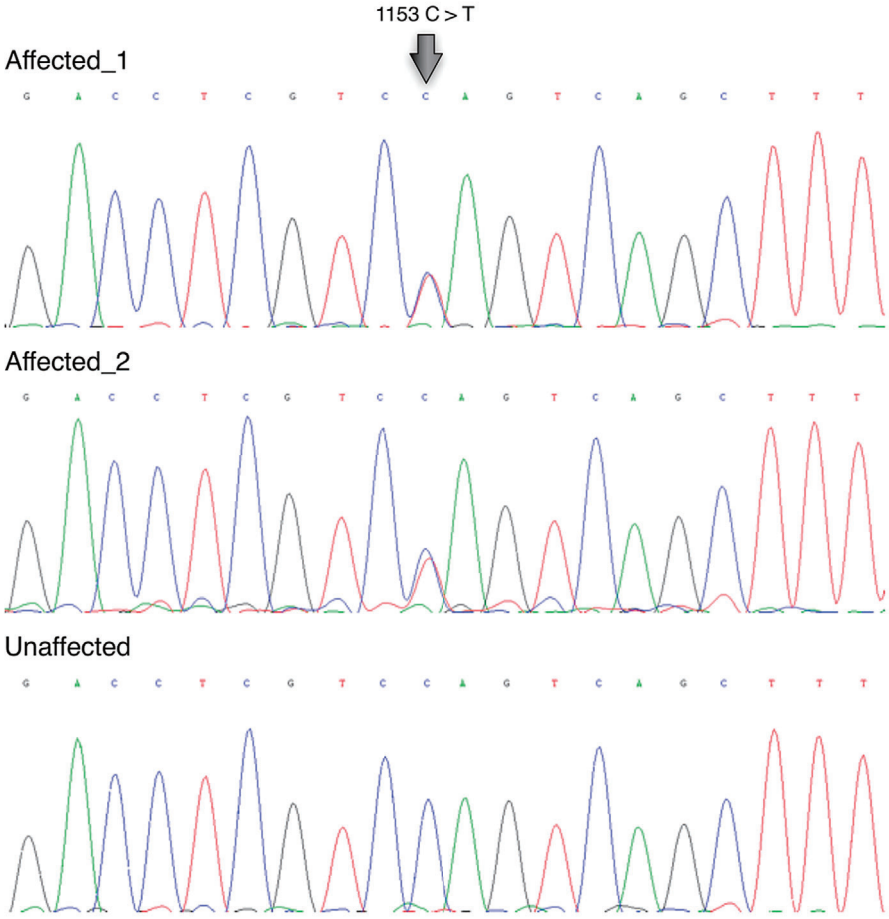

Figure 4. **Identification of a germline heterozygous *FLCN* mutation in two affected patients. The index patient and her affected son showed a heterozygous mutation in exon 10 resulting in a premature termination codon. The unaffected son exhibited the wildtype allele.**

patients from Chinese families. In several analyses of Asian BHDS families, cases of renal neoplasms were found to be rare (13-18). In the present Chinese BHDS family, one of the two affected individuals, the 67-year-old index patient, met the criteria for the full-blown BHDS clinical triad, including multiple skin lesions, pulmonary bullae and clear cell renal cell carcinoma. To our knowledge, this is the first report of a Chinese BHDS pedigree with renal neoplasms and the fifth report of Asian BHDS cases involving all three phenotypes (19).

At present, it is thought that BHDS has only one causative gene, *FLCN*, with various mutations having been identified along the entire length of the coding region (4). Although the detection of mutations in this gene is a critical

standard for making the diagnosis, patients from the same BHDS-affected family, even harboring the same *FLCN* germline mutation, may have different clinical symptoms. Thus far, no particular genotype-phenotype correlations have been confirmed (3, 10, 20). Furthermore, Kunogi et al. suggested that there are population differences in the mutation spectrum of *FLCN* (13). These authors found that Caucasian patients tended to have c.1278dupC or c.1278delC in the mononucleotide tract of eight cytosine resides in exon 11. Meanwhile, c.1347_1353dupCCACCCT in exon12 and c.1533_1536delGATG in exon13 are the most frequently reported mutationsin Japanese patients (13, 18).

The mutation observed in this family, c.1153 C>T, was predicted to truncate the protein product. This is the first report of this mutation in a Chinese family, although it was recently documented in the *FLCN* mutation database ina Japanese case (21). Although all patients in the present family had this substitution, the younger son did not have BHDS-associated renal tumors, as the most threatening and relatively late-onset clinical phenotype (4-6). Similar results have also been found in Asian populations, and Kuroda et al. indicated that BHDS-associated renal tumors often occur with late onset in Japanese subjects (22). Therefore, we cannot eliminate the possibility that the present 33-year-old son may also develop renal neoplasms in his advanced age; hence, the use of annual CT or MRI scans for renal neoplasm monitoring is recommended for this patient.

The authors state that they have no Conflict of Interest (COI).

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Zhichun Lin and Kenan Gong contributed equally to this work.

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