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Case Report

FLCN gene-mutated renal cell neoplasms: Mother and daughter cases with a novel germline mutation

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Abbreviations & Acronyms
AMPK = adenosine monophosphate-activated protein kinase
BHD = Birt–Hogg–Dubé
HOCT = hybrid oncocyte/chromophobe tumor
mTOR = mammalian target of rapamycin
RCC = renal cell carcinoma

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Abstract: Birt–Hogg–Dubé syndrome is a familial genodermatosis, of which patients frequently develop renal neoplasms, fibrofolliculomas and pneumatocele. Here, we report a mother and daughter with renal neoplasms surgically resected (69 and 46 years-of-age at surgery, respectively). The mother's tumor was diagnosed as an unclassified type renal cell carcinoma associated with microscopic tumorous nodules, whereas the daughter's tumor was a hybrid oncocytic/chromophobe tumor. The germline mutation analysis of the responsible gene, *FCLN* (the *folliculin* gene), showed a deletion of 18 bp in exon 5 (c.332_349del/p.H111_Q116del), predicting an alteration of the amino acid sequence of "HPSHPQ" replaced by a single amino acid, "L". This is a novel germline mutation of the *FCLN* gene that has not been previously reported.

Key words: Birt-Hogg-Dubé syndrome, chromophobe renal cell carcinoma, *FCLN* gene, hybrid oncocytic/chromophobe tumor, mutation, oncocytoma.

Introduction

BHD syndrome is a familial genodermatosis, of which the responsible gene is *FLCN*. Three principal symptoms are fibrofolliculoma of the face, neck and upper limbs, spontaneous pneumothorax caused by rupture of the pneumatocele, and renal tumors.[1] The renal tumors are predominantly oncocytoma, chromophobe RCC and HOCT.[2] The responsible gene, *FLCN*, encodes a protein called folliculin, of which the function remains to be elucidated.[3] Although some investigators have reported *FLCN* mutation in sporadic RCC, its frequency is variable among the literature.[4,5] Here, we report mother and daughter cases of renal tumors bearing a novel germline mutation of *FLCN*.

Case presentation

Mother case

The patient was a 69-year-old woman who was diagnosed with renal cell carcinoma of the right kidney, and received radical nephrectomy. She had also presented multiple pneumatoceles, but not any fibrofolliculoma. The patient is doing well 2 years after the surgery, without adjuvant therapy.

The resected kidney contained two tumors in the upper and lower poles. The tumors were homogenously brownish in color, and measured 5 and 3 cm in diameter, respectively (Fig. 1a).

The two dominant tumors were histologically identical and diagnosed as an unclassified type of RCC, because they were composed of large sized atypical cells with eosinophilic

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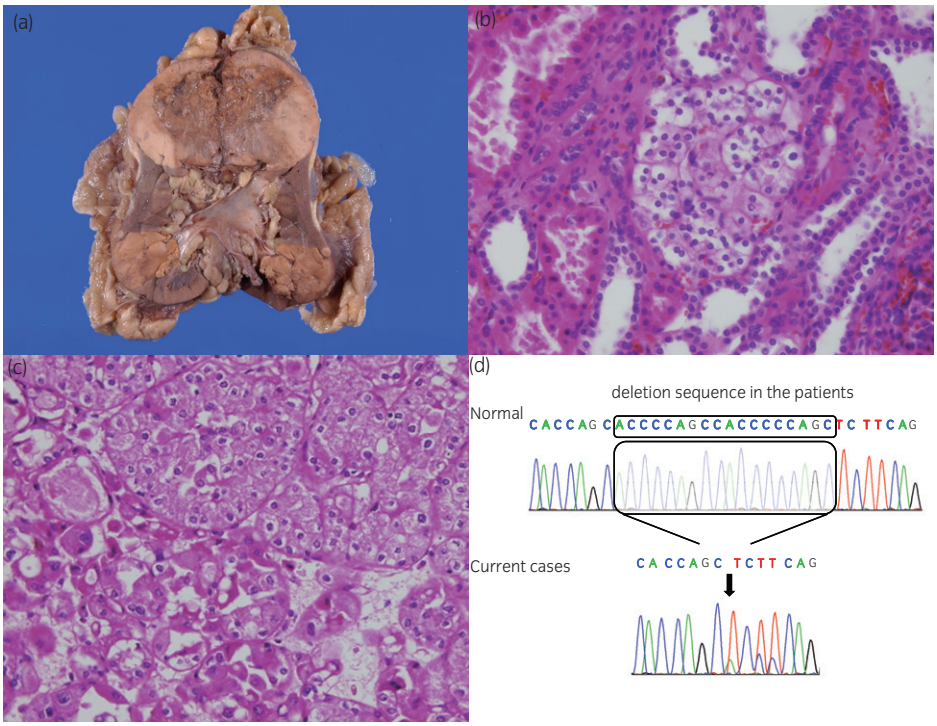

Fig. 1 (a) Gross findings of the resected kidney (mother case). The kidney contained two well-demarcated homogenously brownish tumors in the upper and lower poles. (b) Other than the dominant tumors, small epithelial nests were observed in the mother's kidney. (c) The daughter's tumor was composed of solid and alveolar architectures of polygonal tumor cells with chromophobe and oncocytic cytoplasm. (d) Mutation of the *FCLN* gene (upper, normal; lower, present cases). DNA analysis showed the novel mutation pattern. A total of 18 bp were deleted in exon 5 (c.332_349del/p.H111_Q116del).

cytoplasm, but not characteristic oncocytomatous or chromophobe cells. Other than the two dominant tumors, there were multifocal abnormal cell nests composed of polygonal cells (Fig. 1b).

Daughter case

A daughter of the aforementioned patient showed a renal tumor at 46 years-of-age during radiological examinations, because her mother was suspected to have BHD syndrome. Radiologically, a tumorous lesion in the left kidney was detected along with pneumatoceles in the lungs without fibrofolliculoma. Consequently, partial nephrectomy was carried out. The patient is doing well with periodic follow up 6 months after the surgery.

The resected tumor was well demarcated from the renal parenchyma. The cut surface was homogenously brownish in color. The surgical margin was not involved by the tumor.

The resected tumor was diagnosed as HOCT (Fig. 1c).

Germline mutation analysis of the *FLCN* gene

Written informed consent was obtained from the patients for the analysis of the *FLCN* gene. The study was approved by the Institutional Review Boards of Chiba University and Yokohama City University. The DNA extracted from the peripheral blood cells of the patients were subjected for polymerase chain reaction-based sequencing for mutation analysis of the entire *FLCN* gene, according to a previous report.[6] The genomic DNA of the mother and daughter showed the identical homozygous deletion of 18 bp in exon 5 of the *FLCN* gene (c.332_349del/p.H111_Q116del), predicting an alteration of amino acid sequence of "HPSHPQ" replaced by a single amino acid, "L" (Fig. 1d). This mutation of the *FLCN* gene has as yet never been reported. We also attempted to carry out DNA analyses using formalin-fixed and paraffin-embedded tumor tissue, which were not successful, because of the low quality of the preserved nucleic acid.

Discussion

BHD syndrome is a familial tumor syndrome, of which trias is composed of fibrofolliculoma, pneumatocele causing pneumothorax, and renal tumors.[7] The renal tumors show significantly higher incidence of chromophobe RCC, oncocytoma and HOCT, than those in sporadic cases.

The mother's tumors presented here showed morphological characteristics which could not be classified as a subtype listed in the World Health Organization system.[8] Additionally, the mother case showed multiple abnormal epithelial nests in the renal parenchyma.

The daughter's tumor was diagnosed as HOCT, because of the coexistence of chromophobe and oncocytomatous elements.

The responsible gene, *FLCN*, is a tumor suppressor gene located in chromosome 17p11.2, encoding a protein named folliculin.[3] Although the exact roles of folliculin in renal carcinogenesis remains to be elucidated, recent studies

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showed that folliculin is involved in AMPK and mTOR signaling pathways, and that artificial *Flcn* inactivation in murine kidney generates severe polycystic changes in the kidney.[9,10] Considering these facts, *FCLN* mutation in the present case caused abnormal cell growth in the kidney, resulting in renal epithelial tumors and abnormal cell nests in the mother's case.

Here, we reported renal tumors of unusual histology occurring in a mother and daughter bearing a *FLCN* germline mutation. The mutation was deletion c.332_349del/p.H111_Q116del in exon 5, which has not been previously reported.

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Conflict of interest

None declared.

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