Is Colorectal Neoplasia Part of the Birt-Hogg-Dubé Syndrome?

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ABSTRACT

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant disease originally characterized by the cutaneous triad of multiple fibrofolliculomas, trichodiscomas and acrochordons (skin tags) that usually appear in the third or fourth decades of life[1]. Besides these benign skin tumours this cancer syndrome is characterized by pulmonary cysts, spontaneous pneumothorax, and renal cell carcinoma[2,3]. It is controversial if an increased risk of other internal malignancies is part of the syndrome. Earlier reports have also suggested an increased risk of colorectal neoplasia as part of the syndrome[1,4,5,6]. Recent studies have varied in conclusions and a large epidemiological study from 2002 found no association between colon cancer and BHD syndrome[7].

Here, we report a three generation family with BHD syndrome with a germline mutation in the folliculin gene (FLCN). Two family members were diagnosed with colorectal cancer (CRC). We have been able to demonstrate LOH of the wildtype FLCN allele in colorectal tumors in both family members.

CASE REPORT

A 45-year-old woman (the proband) and her father were referred to genetic counselling from the Department of Dermatology based on skin manifestations suspicious of BHD syndrome.

The proband had developed cosmetically annoying skin lesions in the face from the age of 20. Objective skin examination revealed multiple, small 2-4 millimeter, dome-shaped, firm, skin colored papules with symmetric distribution in the face, on the nose, upper chins and forehead. In addition, axillary acrochordons were found. A skin punch biopsy from the chin showed histological changes...
compatibility with fibrofolliculomas. The proband was otherwise healthy.

The father also had fibrofolliculomas in the face and axillary acrochordons. He had experienced a pneumothorax several years ago after a minor traffic accident. He was moreover diagnosed with two colorectal tumours at age 69. Histology report described two separate adenocarcinomas in rectum and sigmoid with a normal expression of MLH1, MSH2 and MSH6 proteins in the sigmoid tumour.

The proband’s paternal aunt had characteristic skin lesions and had had two spontaneous pneumothoraces in her thirties. At age 59 she was diagnosed with an adenocarcinoma in sigmoid colon and immunohistochemical analyses revealed normal expression of MLH1, MSH2 and MSH6 proteins. She was later diagnosed with a primary lung cancer at age 63 and pathology report described a basoloid carcinoma with focal neuroendocrine differentiation.

Mutation analysis identified a mutation in the FLCN gene (c.1062+2T>G), which previously has been predicted to cause aberrant splicing, since it is located in the conserved splice donor site.

Mutation carriers are shown in the pedigree (Figure 1).

To examine whether LOH was present in the colorectal tumours of both patients, DNA from paraffin embedded normal and tumor tissue was extracted, amplified by PCR and sequenced. Only the sigmoid tumour from the father was examined. The analysis revealed LOH of the wild type allele in both tumor samples as the relative peak area for the FLCN c.1062+2T>G from normal and tumour tissue samples were calculated to be approximately 1:0.8 and 1:0.4, respectively (Figure 2).

**DISCUSSION**

The BHD syndrome is caused by germline mutations in the FLCN gene on chromosome 17 (17p11.2). The gene contains 14 exons and encodes a 579 amino acids protein [9,10,11]. FLCN has recently been shown to belong to a family of Rab guanine nucleotide exchange factors (GEFs). The protein is thought to function as a tumour suppressor gene based on the presence of inactivating FLCN mutations in BHD patients as well as LOH findings in a significant proportion of BHD related tumours [8,12]. A hypermutable polycytosine (C8) tract in exon 11 is a hotspot for germline mutations in this region and 53% of BHD families have mutations [9]. The FLCN mutation 1040

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in this Danish BHD family was a T to G transversion in position +2 in intron 9 and it has been predicted to cause aberrant splicing. This mutation has been found in several Danish BHD families indicating a founder mutation.

The phenotype in BHD syndrome varies between families and there is also intrafamilial variability. It is debated whether CRC is part of the phenotype of BHD. No correlation between the location or type of FLCN mutation and the BHD phenotype has been described[11]. Toro et al[12] did not find a correlation between BHD syndrome and intestinal malignancies in their study of 152 patients in 1999, neither did Zbar et al[13] in a study of 111 BHD patients. Both studies concluded that there is no significantly increased risk of colonic polyps or CRC in BHD patients.

However, several studies have shown an association between BHD and colonic polyps or CRC. Kho et al studied a French three generation BHD pedigree. This family was first described in 1986 and is a large family with 20 family members where 10 persons are assumed to be affected due to typical skin lesions[14]. Kho et al found that six members of the family had colonic polyps and they were all mutation carriers[15]. Furthermore two obligate mutation carriers died of suspected gastrointestinal cancer, but nor DNA nor histology reports were available.

Another case report described a BHD patient with the classic skin tumours, spontaneous pneumothorax, renal cell adenocarcinoma and several adenomas in the colon with severe dysplasia. Genetic studies found a 4 nucleotide deletion in exon 9 of the FLCN gene[16]. There were no reports of CRC among family members.

Latest Kluger et al found a significant link to colorectal pathology in 10 French families with BHD syndrome. Colorectal polyps were diagnosed in 9 patients (50%) but histology reports were not available for all cases. No CRCs were diagnosed[17].

The role of the FLCN gene in unselected sporadic colorectal tumours has been investigated and LOH was found in 81% of the analysed colorectal tumours. The result suggests an involvement of the FLCN gene in tumorigenesis in some microsatellite stable (MSS) sporadic colorectal tumours, and that allelic loss in the region close to the FLCN gene may participate in the progression of colorectal carcinomas[18]. Other data showed that the FLCN gene is involved in microsatellite unstable sporadic CRCs and it was demonstrated that somatic FLCN mutations were present in 5/32 (16%) cases[19].

CONCLUSION

We have been able to demonstrate LOH of the wildtype allele of the FLCN gene in two family members with CRC indicating that this cancer type is part of the phenotypic presentation in this Danish BHD family. This supports an association between CRC and BHD syndrome which has also been concluded recently[11]. It also seems that the FLCN gene is involved in tumorigenesis of sporadic CRCs. Further studies are needed to clarify if colorectal neoplasia is part of the tumour spectrum in BHD families.

CONFICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

1 Birt AR, Hogg GR, Dubé WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol 1977; 113(12):1674-1677
4 Hornstein OP. Generalized dermal perifollicular fibromas with polyps of the colon. Hum Genet 1976; 33: 193-197
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