

Birt-Hogg-Dubé Syndrome

A Novel Marker of Kidney Neoplasia

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Background: Birt-Hogg-Dubé syndrome (BHD) is a dominantly inherited predisposition for development of fibrofolliculomas, trichodiscomas, and acrochordons. Concurrent internal tumors, such as colonic polyps and renal carcinoma, have been described in patients with BHD.

Objective: To evaluate kindreds with familial renal tumors for cutaneous manifestations of BHD.

Design: One hundred fifty-two patients from 49 families underwent complete oral and skin examination. Skin lesions were identified by their clinical appearance, and the diagnosis was confirmed by results of histologic examination. Individuals underwent screening for familial renal neoplasms.

Setting: A tertiary referral research hospital.

Patients: Individuals with familial renal tumors and their asymptomatic at-risk relatives.

Main Outcome Measure: We determined whether any form of renal cancer is associated BHD.

Results: We identified 3 extended kindreds in whom renal neoplasms and BHD appeared to segregate together. Two kindreds had renal oncocytomas and a third

had a variant of papillary renal cell carcinoma. Thirteen patients exhibited BHD. Seven individuals, including a set of identical twins, had renal neoplasms and BHD. An additional 4 patients (3 deceased and not examined) in these families had renal neoplasms but not BHD. Birt-Hogg-Dubé syndrome without renal neoplasms was present in 6 individuals. Thirteen patients with fibrofolliculomas and trichodiscomas presented clinically with multiple smooth skin-colored to grayish-white papules located on the face, auricles, neck, and upper trunk. Oral papules were present in 9 of 28 and acrochordons in 11 of 28 patients. Features of BHD not previously appreciated included deforming lipomas in 5, collagenomas in 4, and pulmonary cysts in 4 of 28 patients. Families with BHD did not display germline mutations in the von Hippel-Lindau gene or in the tyrosine kinase domain of the *MET* proto-oncogene.

Conclusions: Birt-Hogg-Dubé syndrome may be associated with familial renal tumors. Birt-Hogg-Dubé and renal tumors segregate together in an autosomal dominant fashion. Patients with BHD and their relatives are at risk for development of renal tumors. Therefore, patients with BHD and their relatives should undergo abdominal computed tomography and renal ultrasound screening for renal tumors.

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IN 1977, BIRT ET AL¹ described a kindred in which 15 of 70 members over 3 generations exhibited multiple, small, skin-colored, dome-shaped papules distributed over the face, neck, and upper trunk inherited in an autosomal dominant pattern. Histologic examination of these lesions revealed fibrofolliculomas (FFs), trichodiscomas (TDs), and acrochordons. This triad has become known as Birt-Hogg-Dubé syndrome (BHD).¹ Typically, cutaneous lesions of BHD have their onset during the third or fourth decade of life. Since the initial report, several other cases have been described.²⁻¹² The cutane-

ous manifestations of BHD have been associated with colonic polyps^{2,3} and a case of renal carcinoma.⁴ We herein describe 3 kindreds with familial renal tumors in which 13 individuals also had BHD.

Renal neoplasms can be familial or sporadic. Four types of familial renal neoplasms have been well described: (1) clear cell renal carcinoma associated with hemangioblastomas of the brain, spine, and eye resulting from mutations in the von Hippel-Lindau (*VHL*) gene¹³; (2) clear cell renal carcinoma associated with constitutional, balanced translocations involving the short arm of chromosome 3¹⁴⁻¹⁶; (3) papillary renal cell carcinoma associated

PATIENTS AND METHODS

PATIENTS

All patients underwent evaluation at the National Institutes of Health Warren G. Magnuson Clinical Center, Bethesda, Md, and were enrolled in a protocol approved by the institutional review board. Informed consent was obtained from all participants. Two families were included in a previous publication of the renal findings of familial renal oncocytoma.¹⁸ One hundred fifty-two patients ranging in age from 17 to 79 years underwent evaluation from April 1, 1996, to December 31, 1998. All patients underwent complete skin and oral examinations and were photographed. Patients underwent pre- and post-contrast-enhanced computed tomography (CT) of the abdomen followed by renal ultrasound as previously described.¹⁹ Briefly, CT of the abdomen was performed on 1 of 2 units (9800 Quick or GE Hi Speed CT unit; General Electric, Milwaukee, Wis) with the intravenous injection of 120 to 135 mL of iopamidol (Isovue-300; Bracco Diagnostics Inc, Princeton, NJ) after a delay of 70 seconds. Slice thickness was 5 mm, and imaging was performed in a non-helical mode. Available CT scans from other centers were also reviewed in 2 patients. In addition, each patient underwent renal ultrasound using 1 of 2 units (Acuson 128XT; Acuson Corporation, Mountain View, Calif, or Diasonic Spectra; Diasonic, San Jose, Calif). Scanning was performed using a 3- or 5-MHz transducer. Solid lesions seen on results of CT scan and ultrasound suggested the presence of renal tumors. Lesions were considered indeterminate if they were too small (2-5 mm) to be classified as cyst or solid. Individuals without renal tumors on CT findings were classified as not affected. Chest radiographs included posterior-anterior and lateral projections. Histologic criteria for the diagnosis of renal oncocytomas and papillary renal carcinoma were as described previously.^{18,19} In 3 patients, the diagnosis of renal carcinoma was made after review of death certificates, medical records, and pathology and autopsy reports.

with germline mutations in the tyrosine kinase domain of the *MET* proto-oncogene¹⁷; and (4) renal oncocytoma.¹⁸ Pure renal oncocytomas are considered to be benign tumors. Histologically, oncocytomas are composed of cells with an eosinophilic cytoplasm with bland round nuclei and abundant mitochondria as seen on electron microscopy.¹⁸ Papillary renal cell carcinomas have malignant potential, and biological aggressiveness varies with the type. Histologically, papillary renal cell carcinomas have fingerlike projections lined by cuboidal tumor cells with a basement membrane that contains a well-formed fibroconnective tissue stroma.¹⁹ During most of their growth, these renal neoplasms are asymptomatic and are often detected incidentally or through screening of at-risk family members. After noting multiple FFs in a pair of identical twins with bilateral renal oncocytomas, we performed complete skin and oral examinations to search for cutaneous manifestations of BHD in another 150 patients from 49 kindreds with familial renal tumors.

DERMATOLOGIC CRITERIA

Mucocutaneous lesions were diagnosed clinically. The diagnosis was confirmed by results of histologic examination of lesional skin biopsy specimens. We used the following clinical and histologic criteria. Fibrofolliculomas and TDs were multiple, 2- to 4-mm smooth-surfaced, white to skin-colored papules distributed over the face, neck, and upper trunk. Histologically, FFs were defined as multiple anastomosing strands of 2 to 4 epithelial cells extending from a central vellus follicle. A well-demarcated, loose, mucin-rich or thick connective tissue stroma encapsulated the epithelial component.¹ Histologically, TDs consisted of a round to elliptical well-demarcated proliferation of a thick fibrous and vascular stroma in the reticular dermis with a hair follicle at the periphery.¹ Collagenomas were skin-colored to slightly hypopigmented, well-circumscribed indurated papules and plaques. Histologically, collagenomas consisted of a well-demarcated proliferation of thick collagen in the dermis.²⁰ Acrochordons, or skin tags, were soft, pedunculated papules that histologically showed slightly acanthotic and occasionally mild papillomatous epidermis with a loose connective tissue stroma and dilated blood vessels.²⁰ Papules of the oral mucosa were defined as multiple 1- to 2-mm dome-shaped papules involving the lip and buccal and gingival mucosae. Histologically, they were characterized by a collagenous stroma with few fibroblasts.¹⁸ The diagnosis of BHD was made in patients who had 5 or more facial or truncal papules, of which at least 1 papule was confirmed histologically as FF or TD.

MOLECULAR METHODS

The DNA was extracted from peripheral blood leukocytes of patients. The presence of mutations in the *VHL* gene was tested using Southern blotting and sequencing, as previously described.²¹ For screening of mutations of the *MET* proto-oncogene, conformational, sensitive gel electrophoresis was performed, followed by sequencing of exons 16 through 19 of abnormally migrating bands, as described.²²

RESULTS

MOLECULAR STUDIES

Twenty individuals from 18 families with *VHL* had mutation in the *VHL* gene, and 4 individuals from 5 families with hereditary papillary renal cell carcinoma displayed a mutation in the tyrosine kinase domain of the *MET* proto-oncogene. No *VHL* or tyrosine kinase domain *MET* gene mutations were found in 13 patients from 9 families with renal oncocytomas. Families with BHD did not display mutations in the *VHL* gene or the tyrosine kinase domain of the *MET* proto-oncogene or karyotypic abnormalities. The results of mutation analysis in the families with BHD are summarized in the **Table**.

RENAL FINDINGS

We examined 20 affected individuals from 18 families with *VHL* and 6 affected individuals from 5 families with

Dermatologic and Renal Findings in Patients With Birt-Hogg-Dubé Syndrome and At-Risk Relatives Examined at the National Institutes of Health*

	Age, y/ Sex	Dermatologic Findings					Renal History	Renal US or CT	Other Findings	BHD	Molecular Studies	
		FF and/ or TD	ST	OP	C	L					VHL	MET
Family 166												
II:1	61/F	-	-	-	-	-	None	Normal	Melanocytic nevi	-	ND	ND
II:2	65/M	+	+	-	-	-	No surgery	Bilateral solid lesions	CAD, HTN	+	ND	ND
II:3	63/F	-	-	-	-	-	None	Normal	Solar keratosis	-	ND	ND
III:1	41/M	-	+	-	-	-	No surgery	Bilateral renal calculi	CAD	-	ND	ND
III:2	39/M	+	+	+	-	-	Oncocytoma	Bilateral solid lesions	Lung cyst	+	NI	NI
III:3	39/M	+	-	+	-	-	Oncocytoma	Bilateral solid lesions	Lung cyst	+	ND	ND
III:4	36/F	+	+	+	-	-	No surgery	Indeterminate lesions	CHD, PE	+	ND	ND
III:5	42/F	-	-	-	-	-	None	Normal	Dermatofibroma	-	ND	ND
Family 168												
I:1	72/M	+	-	+	+	-	None	Cyst	None	+	ND	ND
I:2	69/M	-	-	-	-	-	None	Cyst	Lung cyst, CAD	-	ND	ND
I:5	75/F	-	-	-	-	-	None	Normal	Nevus spilus	-	ND	ND
II:1	64/M	+	-	+	-	-	Oncocytoma	Bilateral solid lesions	Malignant melanoma	+	ND	NI
II:3	56/F	-	-	-	+	-	None	Normal	None	-	ND	ND
II:5	48/F	+	-	-	-	-	Oncocytoma	Unilateral solid lesion	PDA, BCC	+	NI	ND
III:1	27/M	-	-	-	-	-	None	Normal	None	-	ND	ND
III:7	21/F	-	-	-	-	-	None	Normal	None	-	ND	ND
III:8	25/F	-	-	-	-	-	None	Normal	None	-	ND	ND
III:9	20/F	+	-	+	-	-	None	Normal	Lung cyst, pneumothorax	+	ND	ND
Family 171												
II:3	60/M	-	+	-	-	-	No surgery	Normal	Prostate cancer, BCC	-	ND	ND
II:4	74/M	+	+	+	+	+	Papillary	Solid lesion	Prostate cancer, AVM	+	NI	NI
III:1	35/M	+	+	-	-	+	Papillary	Solid lesion	None	+	NI	NI
III:2	46/M	+	+	+	-	+	None	Normal	None	+	ND	ND
III:3	44/F	-	-	-	-	-	No surgery	Indeterminate	CFM	-	ND	ND
III:4	41/F	+	+	+	-	+	None	Cyst	CFM	+	ND	ND
III:5	49/F	-	+	-	-	-	No surgery	Indeterminate	None	-	ND	ND
III:6	42/M	+	+	-	+	+	None	Normal	None	+	ND	ND
III:7	35/M	-	-	-	-	-	No surgery	1-cm solid lesion	None	-	NI	NI
III:8	37/F	-	-	-	-	-	None	Normal	None	-	ND	ND

*FF indicates fibrofolliculoma; TD, trichodiscoma; ST, skin tags; OP, oral papules; C, collagenomas; L, lipomas; US, ultrasound; CT, computed tomography; BHD, Birt-Hogg-Dubé syndrome; VHL, von Hippel-Lindau; ND, not done; CAD, coronary heart disease; HTN, hypertension; NI, normal; CHD, congenital heart disease; PE, pectus excavatum; PDA, patent ductus arteriosus; BCC, basal cell carcinoma; AVM, arteriovenous malformation; CFM, cutaneous focal mucinosis; plus sign, present; and minus sign, absent. Solid lesions on CT and US findings suggest the presence of renal tumors. Indeterminate lesions are too small to be classified as cysts or solid tumors.

hereditary papillary renal cell carcinoma. We also examined 6 affected individuals from 7 families with clear cell renal carcinoma, 14 affected individuals from 10 families with papillary renal cell carcinoma, and 15 affected individuals from 9 families with renal oncocytomas. No member from families with VHL, hereditary papillary renal cell carcinoma, or clear cell renal carcinoma exhibited cutaneous manifestations of BHD. Two kindreds with renal oncocytomas and a third with a variant of papillary renal cell carcinoma exhibited BHD.

The renal findings of families with BHD are summarized in the Table, and the pedigrees are shown in **Figure 1**. Families 166 and 168 (previously described¹⁸) had affected members with multiple and bilateral renal oncocytomas. Family 166 has 3 individuals with renal neoplasms; III-2 and III-3, identical twins, exhibited bilateral multiple renal oncocytomas, and their father, II-2, had bilateral solid renal lesions on results of abdominal CT. Family 168 has 3 individuals across 2 generations with renal tumors; I-4 (not examined at the National Institutes of Health and, therefore, not included

in the Table) and II-1 had multiple bilateral oncocytomas, and II-5 had oncocytomas on her left kidney. Five individuals in 3 generations from family 171 had renal neoplasms. Family 171 exhibits a variant of papillary renal cell carcinoma without mutations in the tyrosine kinase domain of the MET proto-oncogene. The renal histologic features varied among the affected family members and did not fit readily an existing classic diagnostic histologic category. Surgical pathologic specimens were available for microscopic examination in 2 of these 5 patients. Medical record review revealed that I-1 died when aged 68 years of unclassified renal cell carcinoma, and II-1 died when aged 70 years of bilateral renal tumors, some reported as papillary renal cell carcinoma, some as clear cell renal carcinoma, and some as renal oncocytomas. In the same family, II-4 had a left nephrectomy at age 71 years for a 2.5-cm tumor histologically consistent with a type papillary renal cell carcinoma; III-1 at age 34 years had a right nephrectomy for a 4.0-cm papillary renal cell carcinoma confined within the capsule; and III-7 at age 35 years had a 1-cm solid renal tumor on screening abdominal CT.

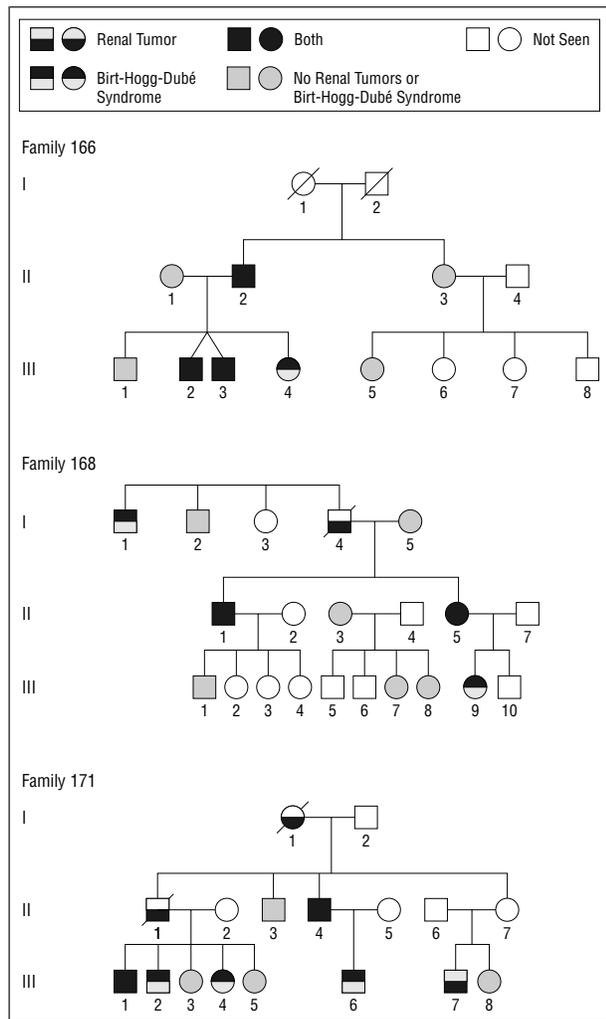


Figure 1. Pedigrees of families affected with renal neoplasms and Birt-Hogg-Dubé syndrome and their at-risk relatives. Squares indicate male members; circles, female; and slashes, deceased.

CUTANEOUS FEATURES

The cutaneous findings in patients from families with BHD are detailed in the Table. Nine men and 4 women ranging from 20 to 79 years of age (mean age, 38.6 years) from 3 kindreds exhibited multiple FF/TD (Figure 1). Clinically, FFs and TDs were indistinguishable; they presented in all patients as multiple, smooth skin-colored to grayish-white papules ranging from 1 to 5 mm in diameter (Figure 2, A and B). In addition, FF/TD presented as comedonal papules in 6 patients and as small cysts on 3 patients. Multiple FF/TD coalescing into a plaque were present on 3 individuals (Figure 2, C and D). All 13 patients had multiple papules on their faces, favoring the nose in 11 (85%), cheeks in 11 (85%), forehead in 8 (62%), and auricles in 4 (31%). Other involved areas included the neck in 10 (77%) and upper trunk in 11 (85%). The number of FFs and TDs ranged from 5 to more than 100. Although some individuals exhibited few papules localized to an area, others had extensive involvement with hundreds of lesions.

Multiple skin tags distributed on the eyelids, periorcular area, neck, axilla, and groin were present in 11

patients from these 3 families (Table). Eight of the 11 patients with skin tags had multiple FFs and TDs. Multiple small, discrete, soft papules involving the lips, buccal mucosa, and gingiva were present in 9 patients (Figure 3, A). Two types of collagenomas were present: atrophic papules and large plaques. Two patients exhibited atrophic papular lesions consisting of groups of white shiny papules less than 4 mm in diameter distributed on the upper or lower trunk. Two patients exhibited dermal plaques greater than 3 cm in diameter. Five patients exhibited multiple lipomas involving up to 30% of the body surface area. One patient showed fat infiltration into muscle on magnetic resonance imaging (Figure 3, B).

DERMATOPATHOLOGIC FEATURES

Sections from 55 skin biopsy specimens obtained from 19 patients were examined using light microscopy. Thirty-five FFs were identified in biopsy specimens (Figure 4). Nineteen biopsy specimens of FFs showed individual or small clusters of immature sebocytes and sebaceous ducts within the epithelial cords. Most (95%) of the biopsy specimens of FFs revealed an epidermis with aberrant follicular structures and thin columns of epithelial cells with and without sebocytes extending into the papillary dermis (Figure 4, B). The epithelial strands were surrounded by a well-demarcated, loose, mucin-rich stroma in 18 specimens (Figure 4, C) and a predominantly thick connective tissue stroma in 17. Sections stained with Alcian blue revealed the presence of mucin within the stroma in all 10 FF biopsy specimens (Figure 4, D). Sections from 4 biopsy specimens exhibited TDs. Five additional biopsy specimens exhibited features of TD and FF. Initial sections showed a thickened collagenous stroma with lamellar fibroplasia around blood vessels adjacent to a hair follicle. Deeper sections revealed a proliferation of cords of epithelial cells emanating from hair follicle characteristic of FF.

Biopsy specimens of lesions with the clinical appearance of collagenomas were obtained in 3 patients. Histologically, these lesions consisted of a well-demarcated proliferation of thick collagen bundles in the reticular dermis. Biopsy specimens of papules from the oral mucosa of 2 patients showed an acanthotic epidermis and dense collagenous stroma with few fibroblasts.

OTHER FINDINGS

Other systemic findings in patients with BHD and their at-risk relatives are summarized in the Table. Four patients had associated neoplasia other than renal, ie, malignant melanoma, prostate cancer, and basal cell carcinoma. In addition, 4 patients from 2 families exhibited pulmonary cysts and/or pneumothorax.

COMMENT

We identified 3 extended families in whom renal neoplasms and BHD appeared to be segregating together. Two families had renal oncocytomas and the third had a type of papillary renal cell carcinoma with oncocytic fea-



Figure 2. Clinical presentations of fibrofolliculomas. *A*, Multiple fibrofolliculomas (FFs) on the nose and paranasal area. *B*, Shiny small papules and papules with a central keratinous plug. *C*, Multiple FFs coalescing into a plaque. *D*, Higher magnification of *C* shows multiple papules with a central keratinous plug with a comedolike appearance.

tures. This type of papillary renal cell carcinoma was not associated with mutations in the tyrosine kinase domain of the *MET* proto-oncogene. Seven individuals, including a set of identical twins, had renal neoplasms and BHD. An additional 4 patients had renal neoplasms without BHD. Three deceased patients with renal neoplasms had not been examined for BHD. Six individuals had BHD without renal neoplasms. Since the onset of FF and TD is earlier than the onset of renal tumors, renal tumors may still develop in these 6 patients. Recently, Roth et al⁴ described a 61-year-old man with BHD and bilateral renal cell carcinoma. Histopathologic examination of renal tissue from this patient revealed an unusual chromophobe adenocarcinoma that consisted of a mixed population of

clear and eosinophilic cells. These findings are very similar to those seen in some of our patients with BHD. This syndrome is associated with various types of renal tumors, and these tumors may constitute a spectrum from oncocytomas to chromophobe to a type of papillary renal carcinoma. The types of renal neoplasms associated with BHD need to be defined better in future studies. Families with BHD did not display mutations in the *VHL* gene or the tyrosine kinase domain of the *MET* proto-oncogene. Birt-Hogg-Dubé syndrome may be due to a single gene mutation leading to skin and renal tumors. It is also possible that different mutations lead to an increased or decreased risk for renal involvement. This may explain why some families have more individuals af-

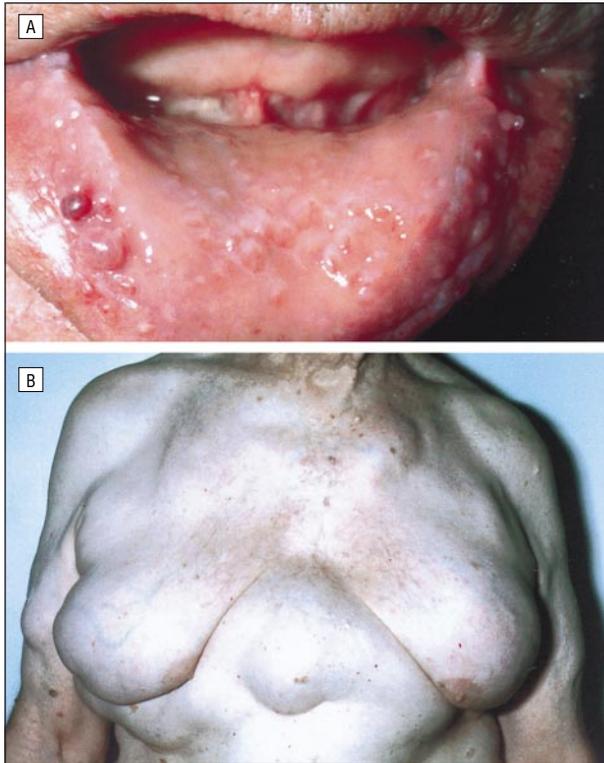


Figure 3. New cutaneous features associated with Birt-Hogg-Dubé syndrome. A, Multiple pedunculated papules on the mucosal surface of the lower lip. B, Multiple large deforming lipomas on the trunk and upper extremities of a man.

ected with renal cancer than others. Because of the autosomal dominant manner in which BHD is transmitted, patients with BHD and their relatives are at risk for development of renal cancer. Therefore, patients with BHD and their relatives should undergo abdominal CT and renal ultrasound screening.

Birt-Hogg-Dubé syndrome has been associated with tumors of various organ systems.¹⁻⁴ In the original family, Birt et al¹ described 1 branch (a sibship of 9) in which 2 dominantly inherited traits occurred. One trait was later known to be multiple endocrine neoplasia type 2 (MEN 2) and was inherited from the paternal line, accounting for the medullary thyroid carcinoma. No evidence of this malignant neoplasm was found elsewhere in the total BHD kindred of 70 family members, and has not been present in BHD patients described subsequently. Recent positional cloning studies of the *RET* gene have revealed that patients from this family who exhibited medullary thyroid carcinoma also displayed a mutation in the *RET* gene (Cheryl Greenberg, MD, oral communication, 1999). Two reports described 2 patients with BHD with polyps in the gastrointestinal tract.^{2,3} In addition, 2 cases of colonic polyps and 1 case of colonic adenocarcinoma have been reported in association with multiple perifollicular fibromas (PFFs).²³⁻²⁵ Perifollicular fibromas have also been reported in BHD. Although colonic polyps have been described in association with multiple acrochordons, various studies have not found a true association of skin tags with colonic polyposis.^{26,27} None of our patients had a history of colonic polyps. However, we did not examine our patients using sigmoidoscopy or colonoscopy. The

association of BHD with colonic polyps needs to be investigated in future studies. We found spontaneous pneumothorax in 1 individual and pulmonary cysts in 4 patients from 2 families (Table). Similar findings, including bullous emphysema and spontaneous pneumothorax, have been associated with BHD.⁹ The infrequent occurrence of these pulmonary findings suggests that they are manifestations of BHD rather than coincidental.

We found 3 families who exhibited cutaneous findings similar to those described in the original report.¹ Multiple FFs were associated with acrochordons in 91% and TDs in 31% of cases of BHD. Several findings suggest that FF and TD represent a spectrum of a single process, rather than 2 distinct dermatological entities. First, the lesions were clinically indistinguishable. Second, we found 5 biopsy specimens that showed features of TD and FF. The diagnosis of FF and TD may depend only on the topographic location of the hair follicle within the biopsy specimen. Also, TD and FF may represent different stages of development of a single process. Recently, it was proposed that PFFs represent transversely cut FFs.²⁸ Most likely, PFFs represent part of the spectrum of FF and TD. Further histologic studies of a large group of patients and identification of the genes involved in BHD may allow us to elucidate how FF, TD, and PFF are biologically related.

Since the original report, a variety of other cutaneous findings have been reported to be associated with BHD.^{6,9,10} We found 2 types of collagenomas: atrophic papular and large plaque. To our knowledge, only 1 other case of BHD associated with collagenomas has been reported.⁶ We identified 5 patients from 1 family who exhibited multiple lipomas involving up to 30% of the body surface area. One patient exhibited fat infiltration into muscle on magnetic resonance imaging. Lipomas had their onset during their third decade of life, similar to the onset of FF and TD. A solitary case of multiple lipomas associated with BHD has been reported.⁹ We also encountered 9 patients from 2 families who exhibited multiple oral mucosal papules similar to those reported by Nadershahi et al.¹⁰ Collagenomas, multiple lipomas, and oral fibromas are infrequent cutaneous findings. This suggests that they represent cutaneous features of BHD.

In addition to BHD, there are several familial tumor syndromes in which the propensity for internal neoplasia is accompanied by the frequent occurrence of cutaneous tumors. These syndromes, such as tuberous sclerosis (TSC), neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 1 (MEN 1), and Cowden syndrome, are caused by the inheritance of mutations in tumor suppressor genes. These genes normally function to suppress cell proliferation and inhibit tumor growth. Tuberin and neurofibromin, the products of the *TSC2* and *NF1* genes, respectively, act in the *ras* signal transduction pathway to regulate cell proliferation and differentiation.²⁹ Menin, the *MEN1* gene product, interacts with the activator protein 1 (AP1) transcription factor JunD and represses JunD-activated transcription.³⁰ The gene mutated in Cowden syndrome, *PTEN*, appears to modulate signaling pathways involving lipid second messengers by functioning as a phospholipid phosphatase.³¹ Loss of the normal function of these proteins is a

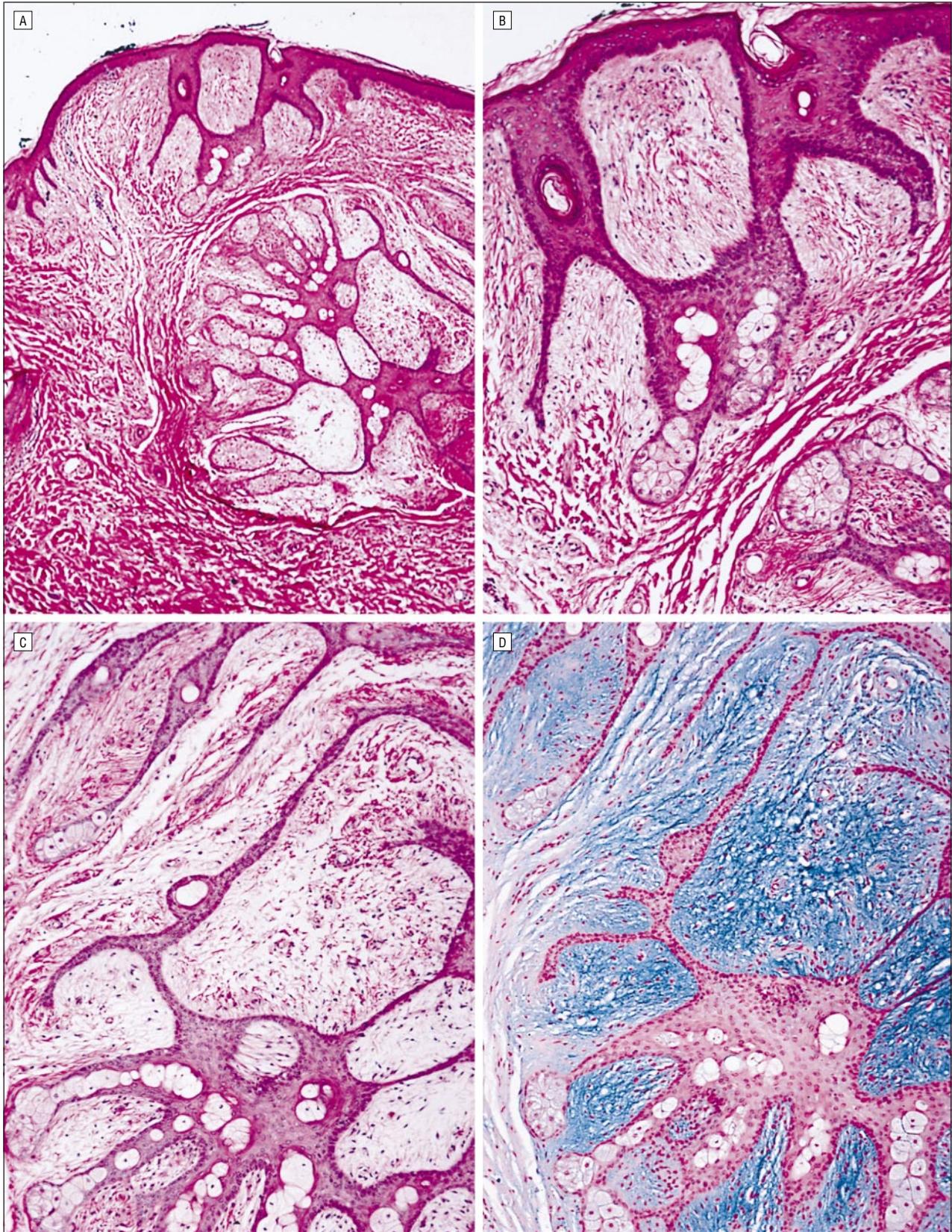


Figure 4. Microscopic features of fibrofolliculomas. A, Multiple anastomosing strands of 2 to 4 epithelial cells extend from the central follicle (original magnification, $\times 100$). B, The underlying epidermis shows aberrant follicular structures with small sebocytes (original magnification, $\times 200$). C, Small sebocytes are within the epithelial structures (original magnification, $\times 200$). D, Alcian blue stain demonstrates the presence of mucin within the stroma (original magnification, $\times 200$).

likely cause for cutaneous tumors in these patients. This involves a second somatic mutation, typically deleting the entire wild-type allele. In MEN 1, for example, angiofibromas, collagenomas, and lipomas develop.³² These cutaneous tumors, like the internal tumors in patients with MEN 1, show allelic deletion of the *MEN1* gene.³³ It is likely that the *BHD* gene functions in controlling cell growth as a tumor suppressor gene. Linkage studies are under way to identify the chromosomal localization for BHD as the first step toward identifying the *BHD* gene. Birt-Hogg-Dubé syndrome may represent another example in which inactivation of a tumor suppressor gene explains the association of cutaneous hamartomas and the internal neoplasia.

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