Birt-Hogg-Dubé Syndrome: Germline Mutation in the $(C)_8$ Mononucleotide Tract of the *BHD* Gene in a German Patient

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Sir,

Birt-Hogg-Dubé syndrome (BHDS) (also known as Hornstein-Knickenberg syndrome in the German literature) is an autosomal dominant inherited skin disease with coexistence of adnexal skin tumours, namely multiple fibrofolliculomas/trichodiscomas and several internal disorders, e.g. renal and colonic neoplasms, and lung cysts. Various other associations may arise incidentally (1–6). The fibrofolliculomas/trichodiscomas are disseminated symmetrically in the face, although neck, shoulder and the trunk can additionally be affected. There is no significant phenotypic overlap of BHDS with other cancer-prone genodermatoses, e.g. Muir-Torre syndrome, Gardner syndrome or Cowden syndrome. Recently, the responsible *BHD* gene was mapped to chromosome 17p11.2 and was identified to encode a 64 kD protein, referred to as folliculin, of so far unknown function (7, 8). Two studies reported germline mutations in the *BHD* gene and suspected a mutational hot spot in a $(C)_8$ mononucleotide tract in exon 11, as frameshift mutations in this mononucleotide tract were found in about 44% of the unrelated patients with BHDS (8, 9). Other germline mutations – located in exons 7, 9 and 12 – were reported only in single BHDS cases (8).

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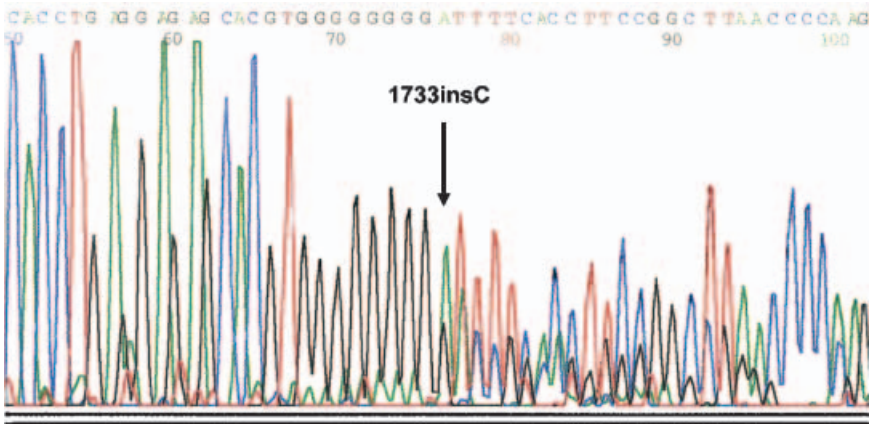

Fig. 1. Germline mutation 1733insC in the $(C)_8$ mononucleotide tract of exon 11 of the *BHD* gene which is predicted to truncate the protein (family 2). The figure shows the antisense strand of the DNA sequence containing the altered poly C tract.

To check the presumed mutational hot spot, we evaluated the $(C)_8$ mononucleotide tract of the *BHD* gene for germline mutations in three unrelated German patients with clinically proven BHDS. The phenotypes of all three index patients met the definition of BHDS, i.e. the occurrence of multiple fibrofolliculomas/trichodiscomas. Clinical characteristics of these three patients and their affected relatives were published recently (2, 5, 10). In all three families the index patients and at least one first degree relative were affected with histologically verified fibrofolliculomas. In addition, colorectal adenomas were found in two index patients and two affected parents died as a consequence of colorectal cancer. For mutation analysis of the $(C)_8$ mononucleotide tract in exon 11 of the *BHD* gene the PCR conditions and primer sequences (SKA7: 5′GGTTCCACTTTGGGCC TGAG; SKA8: 5′GGTAGTAGAGCATGGATGGCC) described by Nickerson et al. (8) were used. Sequencing was performed on an ABI 377 DNA Sequencer (Applied Biosystems). Whereas neither of the index patients in references 2 and 10 showed a frameshift mutation in the mononucleotide tract, in the third patient (5) the frameshift mutation 1733insC could be identified (Fig. 1). This insertion is predicted to truncate the protein 26 missense amino acids downstream.

Our findings support the importance of the $(C)_8$ mononucleotide tract in exon 11 of the *BHD* gene in the aetiology of BHDS, as the majority of *BHD* germline mutations were C insertion or deletion mutations in this mononucleotide tract (8, 9, authors' own data). The high prevalence of these germline mutations raises the possibility of establishing a simple, rapid and cost-effective molecular screening test for patients suspected of BHDS.

Furthermore, in accordance with more recent studies performed by Schulz & Hartschuh (5) we found an increased frequency of extracutaneous manifestations, especially colonic neoplasms, in our families with BHDS. This observation points out the necessity of screening these patients at regular intervals by colonoscopy to prevent the development of colorectal cancer. Conversely, all patients affected with colorectal adenomas and carcinomas should be carefully examined for cutaneous manifestations and asked for their family tumour history.

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