Late Onset of Skin Manifestations in Birt-Hogg-Dubé Syndrome with FLCN Mutation p.W260X

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Birt-Hogg-Dubé syndrome (BHD) (1) is currently defined as an autosomal dominant disorder predisposing for fibrofolliculomas, lung cysts, spontaneous pneumothorax and renal cancer, but clinical expression is highly variable. Further associations with other malignancies have been described, but it remains uncertain whether they are part of the syndrome or merely coincidental (2).

BHD is caused by germline mutations in a novel gene, the FLCN gene, encoding for the protein folliculin (3), whose functions remain unclear. The mammalian target of rapamycin (mTOR) pathway has been implicated in the pathogenesis of BHD, just as in several other hereditary hamartoma syndromes (4, 5). Yet, opposite and conflicting evidence of the role of FLCN in mTOR signalling/phosphorylated ribosomal protein S6 (p-S6) activation has been reported (6, 7). FLCN has been shown to act as a general tumour suppressor in the kidney in a mouse model (7). One mechanism might be that, in the absence of FLCN, an increased hypoxia-inducible factor (HIF) transcriptional activity occurs (8). As HIF influences angiogenesis and cellular metabolism as well as cellular proliferation, it seems to play a central role in tumour growth in inherited diseases that give rise to renal cell carcinoma (8).

The FLCN gene is composed of 14 exons. Germline insertion or deletion of a cytosine in the polycytosine (C8) tract in exon 11 of the BHD gene has been detected in 53% of BHD families and is considered as a mutation “hot spot” (9). More than 40 unique mutations in BHD have been reported, all affecting exons 4 to 14 and flanking intronic borders (10). The FLCN germline mutation c.779G>A that leads to a premature stop codon (p.W260X) had been found previously in a Swiss family reportedly presenting with lung cysts only (11). In all three members of the Swiss family carrying the p.W260X mutation, no skin changes or kidney manifestations were described. Isolated familial spontaneous pneumothorax has also been found in association with two other mutations of the FLCN gene, one nonsense mutation and one 4-bp deletion (12, 13). We describe here a patient and his family in which FLCN mutation p.W260X is associated with a wider range of BHD manifestations in different organs.

CASE REPORT

A 48-year-old man developed pruritic papules around the nose, on the forehead, behind the ears and on the neck at the age of approximately 40 years, growing to a size of approximately 4–5 mm and increasing rapidly in number (Fig. 1a). Four years later, he presented to our clinic with pruritus and desiring cosmetic therapy for the unsightly papules. Based on the clinical appearance, the lesions were diagnosed as fibrofolliculomas, which was subsequently confirmed by histopathology (Fig. 1b). The diagnosis of BHD was established and confirmed by genetic testing. Computer tomography revealed multiple lung cysts (Fig. 1c) and a lipoma of the right kidney. The patient had no history of spontaneous pneumothorax. His 51-year-old brother was also diagnosed with BHD in our hospital. He developed facial papules, also with a late onset, when about 40–45 years old. Furthermore, he had spontaneous pneumothorax twice, at age 35 and 36 years. Our patient’s father had died 20 years previously at age 53 years from unknown causes. Both he and his father (the grandfather of our patient) had similar facial papules.

Direct sequencing of all coding regions and the adjacent splice sites of the FLCN gene revealed the heterozygous nonsense mutation p.W260X in both the index patient and his affected brother (Fig. 1d). This mutation has already been functionally tested and shown to markedly reduce the mRNA level (11). The underlying mechanism is unknown, but it could be a result of nonsense-mediated decay. Heterozygosity for FLCN mutations seems to be sufficient to cause aberrant cell division that results in skin and lung lesions, while the renal tumours in BHD patients might have somatic loss of heterozygosity or point mutations as second hits in the remaining wild-type allele (14).

DISCUSSION

Our patient and his affected brother show that mutation p.W260X can cause most of the clinical hallmarks of BHD, including fibrofolliculomas and lung cysts. A lipoma of the kidney, as found in our patient, has not yet been described as part of the clinical spectrum of BHD. The skin lesions started to occur at age 40 and 45 years, respectively, which is approximately 5–10 years later than the mean age of onset reported in the literature. The index patient in the Swiss family reported by Fröhlich et al. (11) had not developed any cutaneous manifestations at age 56 years. However, so far the number of known patients with this mutation is much too low to establish a reliable genotype-phenotype relationship.

Such data might allow a better risk assessment by showing if certain mutations correlate with a higher or lower rate of potentially life-threatening symptoms, such as renal cancer or pneumothorax. First attempts to reveal genotype-phenotype correlations have already raised the question about the risk for colorectal cancer in patients with the FLCN c.1285dupC mutation (15).
Another study found a correlation between the exonic location of the respective FLCN mutation, the size of lung cysts, and the risk of pneumothorax (10).

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REFERENCES