Expanding phenotype of hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis caused by *FAM111B* mutations: Report of an additional family raising the question of cancer predisposition and a short review of early-onset poikiloderma

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Hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP [MIM#615704]) is an extremely rare syndromic form of autosomal dominant poikiloderma. This genetic disorder was first identified in a South African family in 2006.[1] To date, 3 families and 9 independent sporadic cases have been reported.[2-4] Here we report an additional family of POIKTMP and expand the clinical spectrum. We describe, for the first time to our knowledge, a pancreatic cancer in the clinical course in 1 patient. We also address the differential diagnosis of inherited poikiloderma and related disorders.

Abbreviations used:

IPMN:	intraductal papillary mucinous neoplasm
POIKTMP:	hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis
RTS:	Rothmund-Thomson syndrome

CASE SERIES

In 2007, at the Strasbourg University Hospital, the department of medical genetics referred a family to the dermatology department with a diverse clinical skin picture, dominated by poikiloderma. The father, a white 64 year old, was the sixth (I: 6) of sibship born from nonconsanguineous parents. Very soon after birth, his grandmother observed that "he was not like the others," and he was described to have red cheeks and heat (but not sun) intolerance since early childhood. Clinical evaluation found a very severe case of poikiloderma, predominant in the sun-exposed areas, resulting from the combination of skin atrophy, mottled pigmentation with hyperpigmented and hypopigmented lesions, and telangiectasia (Fig 1, *A*). He had a distinct intolerance for heat with marked hypohidrosis. Diffuse xerosis was combined with multiple depigmented macules on the trunk and limbs. The patient reported lymphedema of the lower limbs (Fig 1, *B*) starting in adolescence, complicated by recurrent erysipelas. His feet and hands were small, both affected by tendon contractures (Fig 1, *B*). His nails and teeth were normal. He did not have a history of cataract formation or pulmonary disease. He also had

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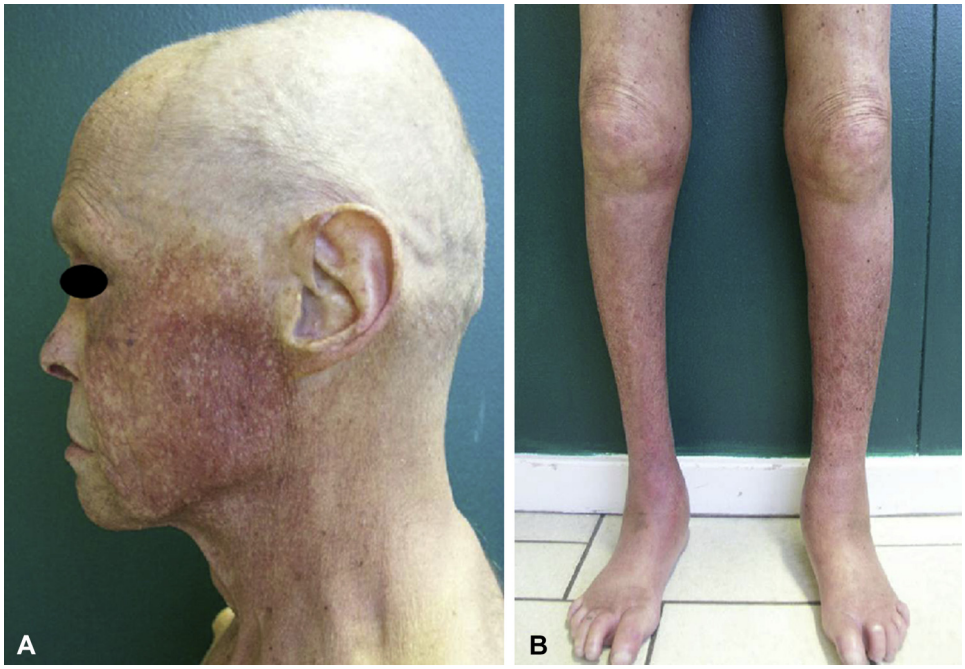

Fig 1. A, Father. Poikiloderma, predominant in the sun-exposed areas but sparing in some zones the forehead and scalp. **B**, Father. Chronic lymphedema of the lower limbs with tendon contractures.

recent-onset alopecia, which was subsequent to chemotherapy. The patient had pancreatic cancer at the time of referral. The appearance of an obstructive jaundice had led, several months earlier, to the diagnosis of pancreatic cancer. A thoraco-abdominal pelvic computed tomography scan found a diffuse infiltration of the pancreas, with peritoneal carcinosis. Magnetic resonance imaging of the pancreas found a tumor in the pancreatic isthmus, with numerous cystic lesions, most likely caused by an intraductal papillary mucinous neoplasm (IPMN). There was no fatty infiltration of the pancreas on magnetic resonance imaging. The diagnosis of invasive adenocarcinoma originating from an IPMN was established by scan-guided pancreatic biopsy. Because of locally advanced stage, only palliative chemotherapy with gemcitabine was administered. The patient had none of the known risk factors of pancreatic cancer such as type 2 diabetes, obesity, pancreatitis, or smoking.

His son (II: 1), age 30, had similar skin changes—red cheeks since 6 months old, developing into an essentially facial poikiloderma; hypohidrosis with heat intolerance; lymphedema of the lower limbs starting in adolescence; guttate leukoderma; and stiffness of the fingers. Teeth, hair, and nails were normal. There was no pulmonary impairment.

His 27-year-old daughter (II: 2) had erythematous cheeks since she was 1 year old. Identical lesions to those of her father were observed: poikiloderma mainly localized to the face; xerosis and innumerable achromic or hypochromic macules, measuring between 1 and 2 mm, of the trunk and the limbs (Fig 2, *A*); marked hypohidrosis; and lower-limb lymphedema. Her hands and feet were small, with atrophy of both thenar and hypothenar eminences (Fig 2, *B*). A biopsy of the palm found marked reduction in eccrine glands, and a biopsy of an achromic macule found a clear decrease in melanin pigment in the basal layer of the epidermis without loss of melanocytes. She had mildly elevated liver transaminases on repeat blood samples, but the search for an etiology was negative. Pulmonary function tests and thoracic computed tomography scan were normal.

Her daughter (III: 3) had facial telangiectatic erythema since the age of 6 months. This family's phenotype, characterized by poikiloderma, hypohidrosis, small feet and hands with tendon contractures or atrophy of the thenar and hypothenar eminences, was reminiscent of the case of a South African family reported in 2006[1] and recently found to have a mutation in the *FAM111B* gene.[5] Sanger sequencing of the family reported herein identified also a mutation in *FAM111B*: p.[Ser628Arg]; [=] c.[1884T>A] (Fig 3) that segregated with the disease confirming that the diagnosis belonged to the POIKTMP spectrum.