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Research Letter

Syndromic inherited poikiloderma due to a *de novo* mutation in *FAM111B*

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Poikiloderma in neonates and infants often presents a diagnostic challenge, with the differential diagnosis including rare inherited disorders such as Rothmund-Thomson syndrome, Bloom syndrome, dyskeratosis congenita, Baller-Gerold syndrome, poikiloderma with neutropaenia, Weary syndrome and Kindler syndrome.[1] Moreover, the differential diagnosis may also include subtypes of porphyria and xeroderma pigmentosum, as well as other rare metabolic, neoplastic, mitochondrial or premature ageing disorders, including Werner syndrome. Recently, a new form of poikiloderma has been described: hereditary fibrosing poikiloderma with tendon contracture, myopathy, and pulmonary fibrosis (POIKTMP).[2] This is an autosomal dominant condition which was shown by whole exome sequencing (WES) to result from mutations in *FAM111B* (Homo sapiens family with sequence similarity 111, member B), encoding a trypsin-like cysteine/serine peptidase.[2,3] FAM111B has also been implicated in other pathology, including exocrine pancreatic dysfunction and susceptibility to prostate cancer.[4,5]

The main clinicopathological features of POIKTMP comprise early-onset poikiloderma, ectodermal dysplasia anomalies, muscle contractures, myopathy, pulmonary fibrosis, growth retardation, liver impairment, exocrine pancreatic insufficiency, cataracts and haematological abnormalities.[2,3] To date, 15 families with POIKTMP have been reported in which 5 different pathogenic missense mutations in *FAM111B* have been identified.[2,3] Precisely how mutations in *FAM111B* lead to the main histological abnormalities of systemic adiposis and fibrosis, however, is uncertain. Here, we describe a new case of POIKTMP and extend the spectrum of clinical anomalies.

Our case is a 14 year old Kuwaiti girl. She is the youngest of 12 siblings born to related parents (2nd degree cousins), but with no family history for any similar disorder. She was born at full term after an uneventful pregnancy, with a birth weight of 3.0kg, and there were no immediate perinatal abnormalities. After a few days, however, she was noticed to have flushing on the cheeks with a recurrent papulovesicular facial eruption (Fig. 1a). Thereafter the clinical features (Fig. 1b-d) have comprised: height and weight below 5th percentile; progressive generalized poikiloderma since early infancy (accentuated in exposed sites); worsening non-scarring alopecia affecting scalp, eyebrows and eyelashes; recurrent gingivitis followed by poor dentition; persistent photosensitivity and heat intolerance; intermittent bony aches (limbs); sclerosis affecting the nose, fingers and toes; and hypothyroidism (on thyroxine replacement). Other normal or negative findings include: normal intelligence; no respiratory abnormalities; no muscle weakness or wasting; no tendon abnormalities or joint contractures. Investigations revealed hypocalcaemia (adjusted calcium 1.71mmol/L; normal 2.20-2.60), low vitamin D (36.8nmol/L; normal 75-250) and mildly impaired renal function (urea 9.5 mmol/L; normal 2.2-6.4: creatinine 108 mmol/l; normal 15-88). Normal or negative findings included: full blood count; anti-nuclear antibodies; complement; zinc; porphyrin screen; immunoglobulins; growth hormone; bone scans.

Following informed consent, genomic DNA from the patient was used for WES analysis, using methodology described elsewhere.[6] For disease inheritance, we searched for potentially damaging homozygous, compound heterozygous or heterozygous variants. Given the history of consanguinity, we initially focused on deleterious homozygous variants but found no mutation that might explain the phenotype. Neither did we identify potentially pathogenic mutations in specific genes such as *RECQL4* (mutated in Rothmund-Thomson

syndrome) or other genes implicated in inherited poikiloderma. However, among the heterozygous variants was a *de novo* change in *FAM111B*, the gene recently implicated in POIKTMP.[2,3] Indeed, the specific mutation present in our patient, c.1289A>C (p.Gln430Pro), is identical to one of the 5 previously reported pathogenic mutations.[3] We confirmed its presence in genomic DNA by Sanger sequencing and demonstrated its absence in parental genomic DNA, consistent with a *de novo* dominant mutation (Figure 1e).

The previous individual reported with the mutation p.Gln430Pro (French male) did not have the major clinical manifestations of POIKTMP seen in most of the other affected individuals. Notably, as in our Kuwaiti girl, he had no clinical symptoms of myopathy (pathology was only evident on magnetic resonance imaging in his case). With regard to genotype-phenotype correlation, codon 430 is the most upstream of the known mutation sites; it is located outside of the functional domain, the possibility being that mutations in codons 625, 627 and 628 are associated with an earlier onset of the disease and a more severe phenotype in terms of cutaneous, muscle and/or visceral involvement. Nevertheless, there were differences in our patient compared to the other p.Gln430Pro case with regard to the presence/absence of sclerosis, vesicles, lymphoedema and, most significantly, interstitial pulmonary fibrosis. Our case currently lacks pulmonary abnormalities which were the cause of premature death in the French subject (aged 40 years). Nevertheless, many of the clinicopathological features of POIKTMP may only begin to manifest in teenagers, and therefore the future clinical course of our patient is uncertain, although close monitoring of her lung function is planned. Indeed, the dermatological features across all cases of POIKTMP, including those with the same *FAM111B* pathology are somewhat variable, for example in terms of nail dystrophy, lymphoedema, cellulitis, eczema or ichthyosis-like skin changes, palmoplantar erythema or keratoderma, sclerosis of the digits, and blisters.[2,3] In

summary, this report identifies a new case of POIKTMP to highlight the clinical manifestations of this recently described entity but also how further studies are needed to understand *FAM111B* function and particularly the mechanisms underlying tissue fibrosis.

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Figure legends

Figure 1. Clinical and molecular features of POIKTMP. (a) Aged 3 months, there are signs of some poikiloderma on both cheeks with a resolving papulovesicular eruption; (b) Aged 6 years, generalised poikiloderma, alopecia and growth retardation are evident; (c) Aged 13 years, facial poikiloderma with loss of scalp hair and eyebrows; (d) Aged 13 years, there is some sclerosis of the fingers in addition to acral poikiloderma; (e) Sanger sequencing reveals a *de novo* missense mutation, p.Gln430Pro, in *FAM111B*.