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Kindler Syndrome in Two Indian Adults: Clinical and Molecular Characterization of FERMT1 Mutations

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Abstract

Kindler syndrome (KS; OMIM 173650) is a rare autosomal recessive genodermatosis historically classified under epidermolysis bullosa, though it exhibits distinct clinical and genetic characteristics. Over 70 mutations in the FERMT1 gene have been identified globally, including point mutations, insertions/deletions, and larger rearrangements. We report two Indian male patients (aged 30 and 31 years) born of consanguineous marriages presenting with hallmark features of KS including trauma-induced blistering, progressive poikiloderma, photosensitivity, mucosal involvement, and nail dystrophy. Genetic analysis via whole-exome sequencing (WES) identified homozygous pathogenic mutations in the FERMT1 gene in both cases. This case highlights the importance of molecular diagnostics in genodermatoses and contributes to the expanding mutational landscape of FERMT1 in South Asia.

Keywords: ***Kindler syndrome; FERMT1; Genodermatosis***

1. Abbreviations

KS: Kindler syndrome; FERMT1: Fermitin family member 1; WES: Whole-exome sequencing; EB: Epidermolysis bullosa

2. Introduction

Kindler syndrome is a rare autosomal recessive genodermatosis first described by Theresa Kindler in 1954 [1]. It is characterized by skin fragility with trauma-induced acral blistering beginning in infancy, photosensitivity (especially in

childhood), progressive poikiloderma with cutaneous atrophy, and eventual mucosal involvement [2]. Affected individuals often have palmoplantar hyperkeratosis and pseudosyndactyly [3]. Mucosal fragility is common, including oral haemorrhages, gingivitis, periodontal disease, leukokeratosis, phimosis, and strictures [4]. KS has an intriguing progressive phenotype; blistering tends to improve after childhood, but poikiloderma and atrophy worsen with age. Severe long-term complications include aggressive squamous cell carcinomas affecting sun-exposed skin and oral mucosa [5].

Due to its overlapping features, KS may be misdiagnosed in early life as dystrophic, junctional, or simplex epidermolysis bullosa, or as other poikilodermatous syndromes like Rothmund–Thomson syndrome. Clinical clues such as cigarette-paper-like wrinkling on acral skin and the improvement of blistering over time can aid in distinguishing KS [6]. However, a definitive diagnosis relies on molecular testing, which is essential not only for accurate diagnosis but also for long-term management and genetic counselling.

Here, we report two classic cases of Kindler syndrome in Indian adult males associated with homozygous pathogenic mutations in exon 5 of FERMT1—one a nonsense mutation (c.599C>G, p.Ser200*) and the other a recurrent frameshift mutation (c.676dup, p.Gln226Profs*17).

3. Case Report

3.1 Case 1

A 30-year-old Indian man, born of a third-degree consanguineous marriage, presented to a tertiary care dermatology clinic with a history of skin discoloration and severe sensitivity to sunlight since childhood. He had history of recurrent blistering over the trunk and extremities, which eventually transitioned into trauma-induced acral blistering and gradually improved with age. Over time, he developed progressive poikilodermatous changes that became prominent during early childhood and persisted into adulthood.

Dermatologic examination revealed prominent poikiloderma characterized by reticulate pigmentation, atrophy, and telangiectasia across the body. The skin was notably xerotic, particularly on the dorsum of the hands and feet, which exhibited atrophic scars and characteristic "cigarette-paper" like wrinkling (FIG. 1). Palmar examination demonstrated keratoderma with blunting of the palmar creases and evidence of pseudosyndactyly (FIG. 2). Mucosal and systemic evaluation showed gingivitis, mild ocular congestion, and phimosis. There was no history of similar blistering disorders in other family members.

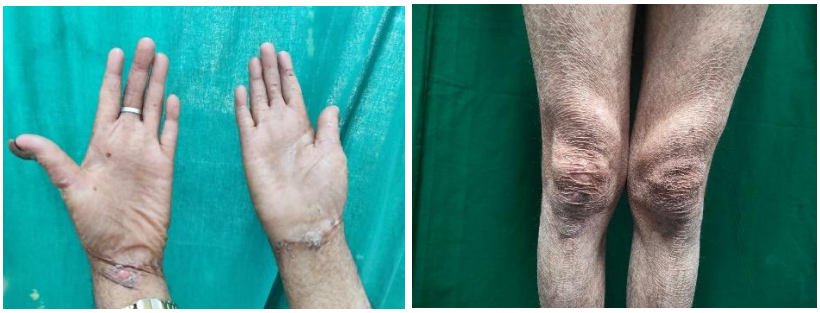

FIG. 1. **Generalized poikiloderma with reticulate pigmentation, cutaneous atrophy, telangiectasia, and xerosis. The dorsum of the hands and feet shows atrophic scars with characteristic "cigarette-paper" wrinkling in Case 1.**

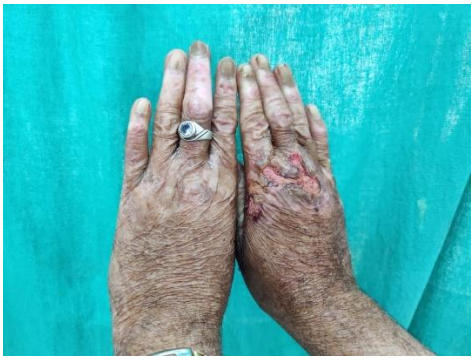

FIG. 2. **Palmar keratoderma with blunting of the palmar creases and pseudosyndactyly in Case 1.**

Routine laboratory tests were unremarkable and systemic examination was within normal limits. A skin biopsy showed epidermal atrophy and pigment incontinence, while electron microscopy revealed splits at multiple levels of the dermo-epidermal junction with a prominent, thick, and wavy lamina densa. Considering Kindler syndrome as a differential diagnosis, genetic analysis via whole-exome sequencing was performed and identified a homozygous pathogenic nonsense mutation, c.599C>G (p.Ser200*) in exon 5 of FERMT1, confirming the diagnosis of KS.

3.2 Case 2

A 31-year-old unmarried Indian man, born of a third-degree consanguineous marriage, presented with a decade-long history of dark discoloration and sensitivity to sunlight. From infancy, he had recurrent blistering over acral sites, which gradually healed with atrophic scars. Over the past ten years, he developed diffuse hyperpigmentation and mottled poikiloderma on sun-exposed skin, and severe photosensitivity. Dermatologic examination revealed generalized poikiloderma with diffuse hyperpigmentation and telangiectasia on the face, neck, and upper trunk (FIG. 3). The skin was notably atrophic and wrinkled ("cigarette-paper" like), especially on the dorsal hands and forearms (FIG. 4). The anterior trunk showed patchy pigmentary changes and atrophic areas (FIG. 5). Palmar examination demonstrated diffuse keratoderma with pronounced fissuring and loss of dermatoglyphics (FIG. 6). Mucosal examination showed gingival erythema and erosion, and dental enamel wear. There was no history of systemic illness or photosensitivity syndromes in the family.

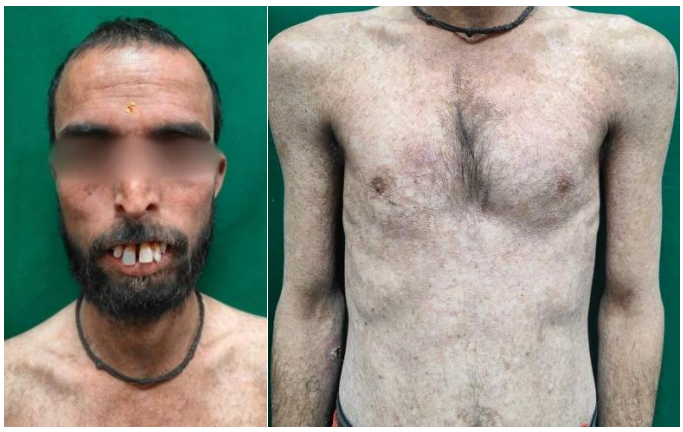

FIG. 3. **Generalized poikiloderma with diffuse hyperpigmentation and telangiectasia involving the face, neck, and upper trunk in Case 2.**

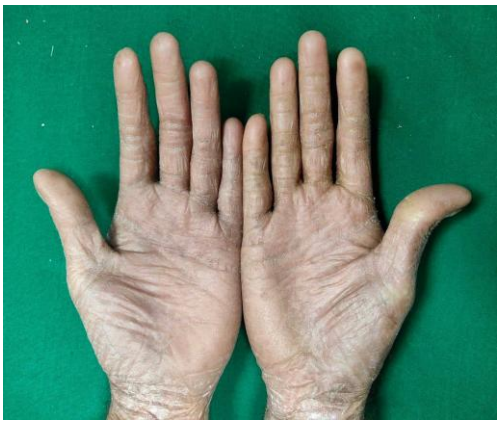

FIG. 4. **Atrophic, wrinkled ("cigarette-paper") skin over the dorsal hands and forearms in Case 2.**

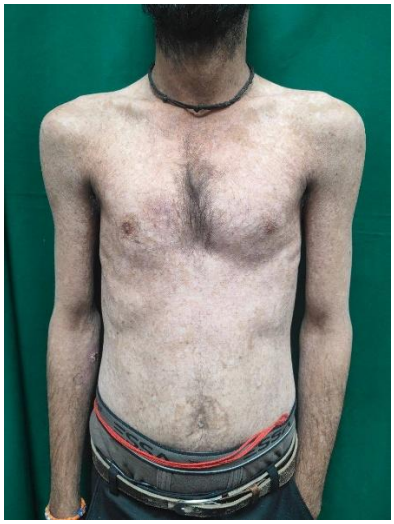

FIG. 5. **Patchy pigmentary changes with cutaneous atrophy over the anterior trunk in Case 2.**

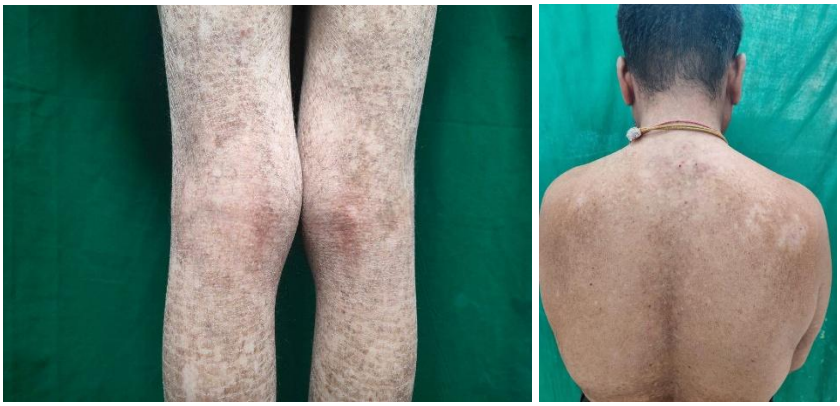

FIG. 6. **Diffuse palmar keratoderma with fissuring and loss of dermatoglyphics in Case 2.**

Routine laboratory tests were unremarkable. A skin biopsy from a hyperpigmented lesion showed marked epidermal atrophy, melanophages (pigment incontinence), and prominent dilated superficial dermal blood vessels, consistent with poikiloderma (FIG. 7).

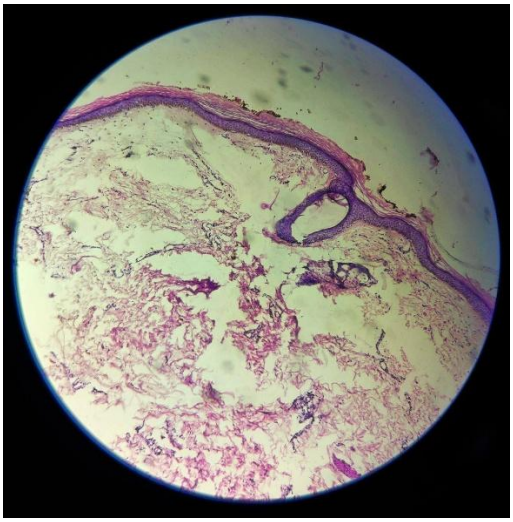

FIG. 7. **Histopathological examination showing epidermal atrophy, pigment incontinence with dermal melanophages, and dilated superficial dermal blood vessels, consistent with poikiloderma (Hematoxylin and eosin stain, original magnification ×100).**

Considering Kindler syndrome as a differential diagnosis, genetic analysis via whole-exome sequencing was performed and identified a homozygous pathogenic frameshift mutation, c.676dup (p.Gln226Profs*17) in exon 5 of FERMT1, confirming the diagnosis of KS.

4. Discussion

Kindler syndrome is caused by mutations in the FERMT1 gene (also known as KIND1), located on chromosome 20 [7]. This gene encodes kindlin-1, a FERM-domain-containing protein critical for integrin signalling [7]. Kindlin-1 plays a vital role in anchoring the actin cytoskeleton to the extracellular matrix. Its absence disrupts integrin-mediated keratinocyte adhesion and impairs cytoskeletal organization, setting KS apart mechanistically from other forms of epidermolysis bullosa (EB), which involve structural proteins of the basement membrane zone or hemidesmosomes [8].

In Case 1, whole-exome sequencing revealed a homozygous pathogenic nonsense mutation, c.599C>G (p.Ser200*) in exon 5, resulting in a stop codon and premature truncation of the kindlin-1 protein at codon 200. This specific variant, though not previously reported in literature, is similar to known pathogenic loss-of-function mutations in FERMT1. In Case 2, genetic analysis identified a homozygous pathogenic frameshift mutation, c.676dup (p.Gln226Profs*17) in exon 5, which creates a premature stop codon 17 residues downstream of codon 226.

Both mutations occur in exon 5, which is critical for the FERM/PH architecture of kindlin-1; these truncations are predicted to abolish integrin-binding and co-activator functions [9]. Disruption of integrin signalling results in impaired keratinocyte adhesion, explaining the characteristic cutaneous and mucosal fragility observed in both patients [10].

To date, more than 70 distinct pathogenic FERMT1 variants have been reported worldwide, with loss-of-function being the predominant mechanism (TABLE 1). While the nonsense mutation in Case 1 appears to be a rare "private" mutation, the

c.676dup variant in Case 2 represents a recurrent hotspot documented in multiple unrelated cases globally [11-13]. Population data from gnomAD indicates that the c.676dup variant is rare, with an allele frequency of approximately 0.11% in South Asian cohorts.[8]

TABLE 1. **Selected FERMT1 Mutations Reported in Kindler Syndrome [7-10].**

HGVS_c	Protein	Variant Type	Reported Countries
c.676dup (NM_017671.4)	p.(Gln226Profs*17*)	Frameshift (dup)	Pakistan; Brazil; multiple cohorts
c.811C>T	p.(Arg271Ter)	Nonsense	East Asia; multiple reports
c.910G>T	p.(Glu304Ter)	Nonsense	Iran, Germany, Australia, Italy
c.328C>T	p.(Arg110Ter)	Nonsense	India (case series)
c.277C>T	p.(Gln93Ter)	Nonsense	Various European reports
c.936del	p.(Met312fs)	Frameshift deletion	ClinVar/LOVD
c.1714_1715insA	p.(Val572fs)	Frameshift insertion	Literature/ClinVar
c.1867_1869del	p.(Ile623del)	In-frame deletion	ClinVar/variant lists
c.1371+4A>G	–	Splice-site (intronic)	Europe/Asia
c.892_893insALU	–	ALU insertion (structural)	Various reports
Large deletions/CNV	–	Large deletions	Italy, China
Deep intronic variants	–	Cryptic exon splicing	Europe

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