Dermatology Practical & Conceptual

# A Spontaneous Novel c.679dupG Mutation in the LOR Gene Resulting in Loricrin Keratoderma with Ichthyosis

Divya Bhalla[1], Vamsi K. Yenamandra[2], Tanvi Dev[3], Vishal Gaurav[3]

**1** CSIR-Institute of Genomics and Integrative Biology, New Delhi, India
**2** Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, India
**3** Department of Dermatology and Venereology, Maulana Azad Medical College, New Delhi, India

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**Corresponding Author:** Tanvi Dev, MD, Assistant Professor, Department of Dermatology and Venereology, Maulana Azad Medical College, New Delhi, India. E-mail: ivnat2008@gmail.com

## Introduction

Palmoplantar keratoderma (PPK) encompasses a heterogeneous group of keratinizing disorders with diverse clinical phenotypes. Loricrin keratoderma (LK) is a distinct form of hereditary PPK caused by pathogenic variants in the *LOR* gene, which encodes loricrin, a key protein in the epidermal cornified envelope (CE) [1]. We describe a patient with a classic LK presentation and a novel duplication mutation in *LOR*.

## Case Presentation

A 20-year-old female, born to non-consanguineous parents, presented with thickened palms and soles, generalized skin dryness since birth, and heat intolerance with erythema during summers (Figure 1A–G). She was born encased in a collodion membrane, which resolved within two months. No family history of similar skin disorders was reported. Examination revealed a thin-built, malnourished habitus with diffuse honeycomb-patterned palmoplantar hyperkeratosis and painful constriction bands on bilateral little toes and fingers. Marked hyperkeratosis was observed over knuckle pads, proximal interphalangeal joints, elbows, and the Achilles tendons. Well-demarcated hyperkeratotic plaques were noted over the wrists and flexures, including the axillae, cubital, and popliteal fossae. Generalized ichthyosis presented as fine, white, semi-adherent scales which were larger and darker on the neck and chest, giving a parchment-like appearance. Scalp, genital, nail, mucosal, and systemic examinations were unremarkable. A skin biopsy from the palm showed hyperkeratosis, acanthosis, and prominent keratohyalin granules. Based on clinical findings, LK was suspected. Whole exome sequencing (WES) was performed after obtaining informed consent. Genomic DNA from the patient was analyzed using the Twist Exome 2.0 Plus Comprehensive Exome Spike-in

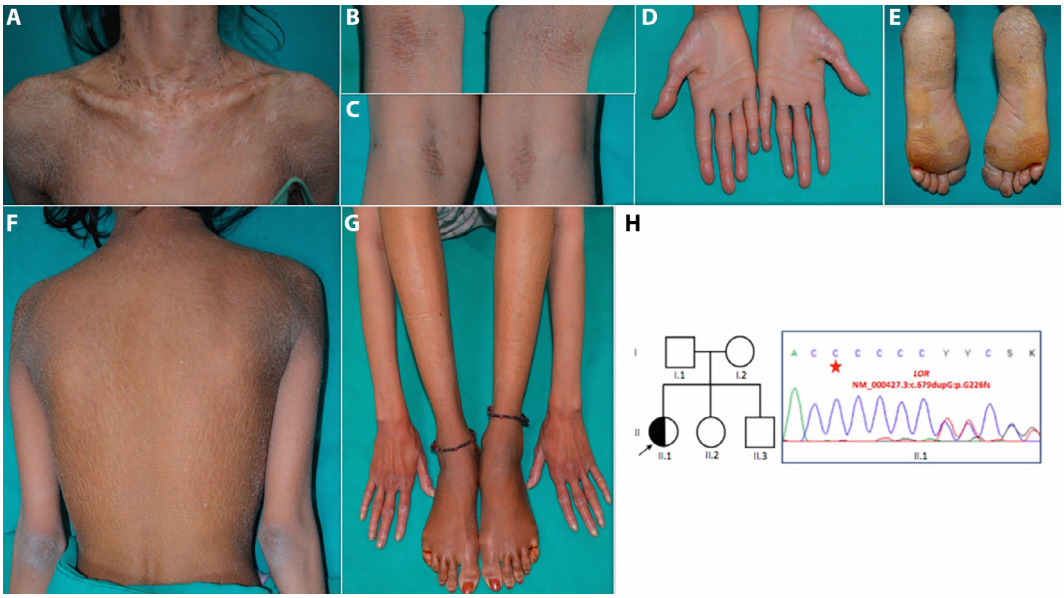


**Figure 1.** A) semi-adherent coarse scales over neck, upper chest, and bilateral shoulders, B) hyperkeratotic plaques in cubital fossa, C) and popliteal fossa, D,E) diffuse palmoplantar keratoderma, F) fine white-colored semi-adherent scaling over back, arms and elbows, G) along with hyperkeratotic plaques over knuckle pads and pseudoainhum involving bilateral little toes, H) and pedigree of the family and sequence chromatogram depicting the identified heterozygous variant in the patient.

library kit (Twist Biosciences, USA) on an Illumina platform. A heterozygous pathogenic duplication mutation in exon 2 of *LOR* (c.679dupG:p.Gly226fs) was identified (Figure 1H). This variant was absent in population databases, including 1000 Genomes, gnomAD, and Indigen. No additional pathogenic variant in genes associated with PPK or ichthyosis was detected. Sanger sequencing confirmed the presence of this variant in the patient.

## Conclusions

LK is characterized by diffuse PPK with a honeycomb pattern, generalized ichthyosis, and in some cases, digital constriction bands (pseudoainhum), which can lead to auto-amputation. Some patients are born with a collodion membrane, expanding the phenotypic spectrum [2]. However, overlapping features with other keratinizing disorders pose diagnostic challenges [3]. Our patient exhibited hallmark features of LK. The identified frameshift mutation (c.679dupG:p.Gly226fs) occurs in a previously recognized mutational hotspot, a stretch of six consecutive guanine nucleotides [4]. Other pathogenic variants in this region have been reported, including c.678_679dupG:p.Ser229ValfsTer107, with differences likely due to annotation discrepancies [5]. This duplication mutation has not been previously described. Mutations in this G-rich region, such as 730insG, have been associated with variable severity [3]. Prior studies indicate that single-nucleotide insertions in this region lead to premature termination, causing aberrant nuclear accumulation of the mutant loricrin protein instead of its integration into the CE. This disruption impairs keratinocyte differentiation and apoptotic regulation, compromising skin barrier function and leading to the LK phenotype [2].

In conclusion, we report a novel *LOR* gene mutation, expanding the genetic spectrum of LK. This finding contributes to understanding its molecular pathogenesis and phenotypic variability.

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