SHORT COMMUNICATION

Novel TP63 Mutation (c.1768C>T, p.Pro590Ser) Expands the Phenotypic Spectrum of TP63-related Disorders: Severe Palmoplantar Hyperkeratosis, Ectodermal Dysplasia, and Cutaneous Squamous Cell Carcinoma

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TP63-related disorders comprise a spectrum of rare autosomal dominant conditions characterized by abnormal development of ectodermal derivatives (1). The TP63 gene encodes a critical transcription factor for epithelial development, and its mutations lead to several distinct syndromes with overlapping features, including EEC (ectrodactyly, ectodermal dysplasia, cleft lip/palate), AEC (ankyloblepharon, ectodermal dysplasia, cleft lip/palate), and ADULT (acro-dermato-ungual-lacrimal-tooth) syndromes (2, 3). The specific phenotypic manifestations are strongly influenced by the location of the mutation within the functional domains of the p63 protein (4–6). Here, we report a case with a novel TP63 mutation presenting with a severe and complex phenotype, challenging straightforward classification into existing syndromic entities.

CASE REPORT

A 68-year-old Asian male presented with lifelong generalized cutaneous abnormalities. His history was significant for complete anodontia following primary tooth exfoliation at age 6, progressive alopecia leading to total scalp hair loss by age 30, and marked hypohidrosis. At age 60, he developed a cutaneous squamous cell carcinoma (SCC) in the pubic region, which was successfully treated with surgical excision. Physical examination revealed widespread xerosis with pruritic papules and dyschromia, severe palmoplantar hyperkeratosis with painful fissuring and haemorrhage (**Fig. 1**A, B), and dystrophy of all fingernails and toenails (**Fig. 1**C, D). Notably, there was no evidence of ectrodactyly, syndactyly, or orofacial clefting. Ophthalmic examination confirmed the absence of ankyloblepharon. No similar phenotype was reported among his deceased parents or 3 siblings.

Genomic DNA was extracted from peripheral blood lymphocytes. Clinical whole-exome sequencing (WES) was performed using a PCR-free library preparation followed by sequencing on an Illumina platform. The mean coverage of the nuclear genome was 30×, with ≥98% of the genome covered at ≥10× and≥90% covered at ≥90×. Sequence reads were aligned to the UCSC hg19 reference genome using BWA, and variant calling was performed following the GATK best practices. A heterozygous missense variant in exon 14 of TP63 (NM_003722.5), c.1768C>T, was identified, leading to the amino acid substitution p.Pro590Ser within the transcriptional inhibitory domain (**Fig. 2**). This variant was absent in population databases (ExAC and gnomAD). Multiple *in silico* prediction tools (PolyPhen-2, SIFT, MutationTaster) consistently supported a deleterious effect. Segregation analysis could not be performed as the parents were deceased and no biological samples were available. However, the absence of a family history and the lack of the variant in population databases strongly suggest that the p.Pro590Ser variant likely occurred *de novo*.

DISCUSSION

We report a novel *de novo* TP63 mutation (p.Pro590Ser) presenting with a complex phenotype of severe ectodermal dysplasia, profound palmoplantar hyperkeratosis, and a history of cutaneous SCC. This case proves challenging to classify and expands the known phenotypic spectrum associated with TID domain mutations.

Our patient's presentation shares features with several TP63-related syndromes but does not conform perfectly to any single classic entity. The presence of ectodermal dysplasia (alopecia, anodontia, nail dystrophy) and the development of SCC are features associated with ADULT syndrome (7). However, the absence of pathognomonic

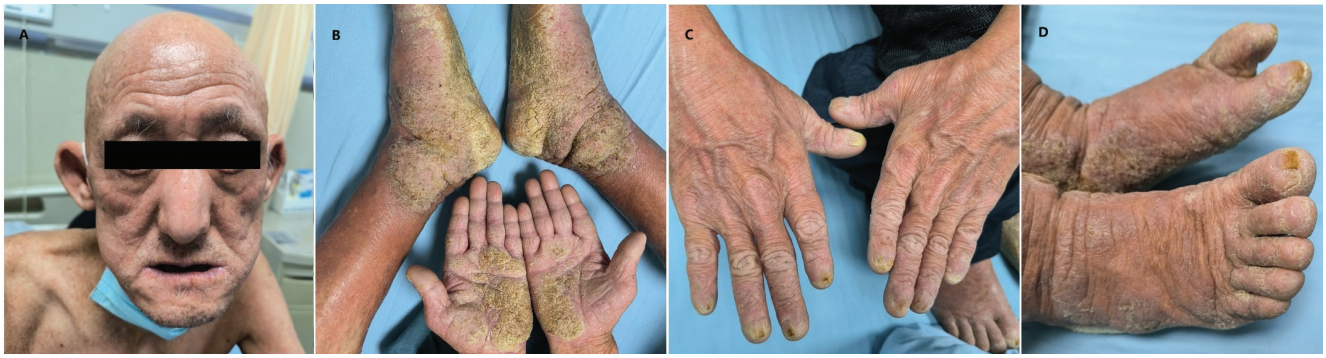

Fig. 1. Clinical manifestations of the patient. (A) Facial features demonstrating complete alopecia, sparse eyebrows, and facial wasting. (B) Severe palmoplantar hyperkeratosis with fissuring and haemorrhage. (C) Dystrophic fingernails. (D) Dystrophic toenails.

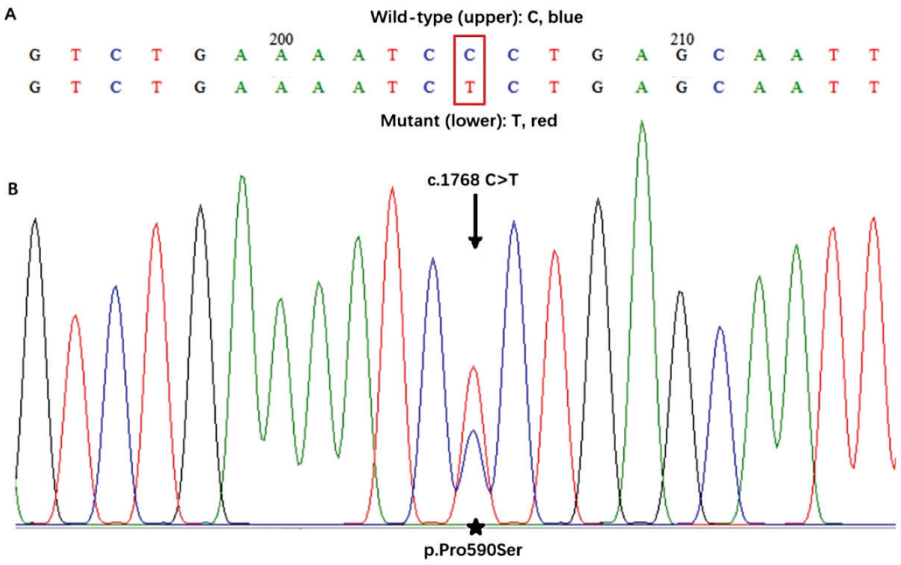

Fig. 2. Identification of a *de novo* heterozygous TP63 variant by whole-exome sequencing. (A) Electropherogram view of the wild-type (upper) and mutant (lower) sequences, generated from WES data. The genomic region of TP63 exon 14 shows a heterozygous c.1768C> T transition (arrow) in the mutant, evidenced by overlapping peaks of the wild-type (C, blue) and mutant (T, red) alleles, compared with the homozygous wild-type C (blue) in the upper panel. (B) Schematic representation of the resultant amino acid change p.Pro590Ser within the transcriptional inhibitory domain of the TP63 protein.

acral anomalies, such as ectrodactyly or syndactyly, which are hallmarks of ADULT syndrome, argues against this specific diagnosis (8). Conversely, the mutation's location in the TID domain is typically linked to AEC syndrome (4, 9). Yet, our patient lacked congenital ankyloblepharon or the severe, erosive scalp dermatitis characteristic of AEC.

The p.Pro590 residue is a recognized mutational hotspot within the TID domain. Previous reports have described substitutions at this same residue, p.Pro590Leu and p.Pro590His, in patients with AEC syndrome (9, 10). Functional studies of these variants have established that mutations at this residue exert a dominant-negative effect, disrupting p63's transcriptional activity and leading to impaired epithelial development (11). The development of cutaneous SCC in our patient aligns with the reported phenotype of other cases with mutations at this residue, underscoring a consistently heightened cancer risk associated with TID domain perturbations. We hypothesize that this shared oncogenic risk stems from the disruption of p63's core role in maintaining epidermal homeostasis and tumour suppression.

We propose that the p.Pro590Ser mutation contributes to the observed severe palmoplantar hyperkeratosis and tumorigenesis through multifaceted mechanisms. As a key master regulator, p63 directly controls the expression of a suite of genes involved in epidermal differentiation and cell adhesion (4). The disruption of these downstream target genes by a dominant-negative p63 mutant would severely compromise skin barrier formation and integrity, clinically manifesting as profound hyperkeratosis and creating a susceptible microenvironment for carcinogenesis (12).

Furthermore, the pathophysiology of TP63-related disorders involves chronic inflammation and barrier defects (4, 12). Notably, persistent inflammatory infiltrates were also observed in the severely hyperkeratotic skin of our patient. The potential role of inflammatory pathways, such as IL-17, in TP63-related phenotypes and how they might contribute to both hyperkeratosis and cancer development represents a compelling area for future investigation (13, 14). The p.Pro590Ser mutation may create a pathological "soil" comprising both developmental defects and sustained inflammation, ultimately permitting the "seed" of SCC to take root (15).

Given that TP63-related disorders are chronic and management is often challenging, there is a critical need for strategies that alter the disease course in patients with a high lifetime risk of SCC. This case suggests that an aggressive management strategy, including early and frequent skin cancer surveillance, is imperative for patients with specific TID domain mutations. Therapies aimed at modulating the aberrant differentiation and proliferation, such as systemic retinoids, could be explored in the future for managing such severe phenotypes (16, 17).

In conclusion, this case of a novel TP63 p.Pro590Ser mutation expands the phenotypic spectrum of TID domain-related disorders. It highlights a severe triad of profound palmoplantar hyperkeratosis, classic ectodermal dysplasia signs, and cutaneous SCC, which cannot be neatly categorized into existing syndromes. This report emphasizes the continuous clinical spectrum of TP63-related disorders and reinforces the importance of considering TP63 mutations in adult patients with severe ectodermal dysplasia and skin cancer, even in the absence of classic limb or facial clefts.

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Ethics statement: All authors agree with the UN's Declaration of Human Rights. Written informed consent was obtained; the study protocol was approved by the Ethics Committee of Zhangzhou Hospital Affiliated to Fujian Medical University (Approval No. 2024LWB024).

All authors have no conflicts of interest to declare.

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