

Papillon–Lefèvre Syndrome Associated with a Newly Identified Homozygous c.872G>A Mutation in the CTSC Gene: A Case Report

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Case Report

History

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ABSTRACT

Papillon–Lefèvre syndrome (PLS) is a rare autosomal recessive genodermatosis caused by pathogenic variants of CTSC gene. The condition is characterized by the coexistence of palmoplantar keratoderma and early onset rapidly progressive periodontitis. Here, we present the case of a 21-year-old female patient in whom a previously unreported homozygous CTSC variant, c.872G>A, was identified.

Since childhood, the patient had marked hyperkeratosis in the palmoplantar region, early tooth loss, and the need for oral prostheses. A family history of individuals with similar dermatologic features and consanguinity between parents supported an autosomal recessive inheritance pattern. The identified variant was evaluated in conjunction with the clinical phenotype and classified as likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria.

Systemic retinoid therapy was recommended, but could not be initiated because of patient preference. This case contributes to the expanding genetic spectrum of PLS and highlights the crucial importance of early diagnosis, multidisciplinary approach, and treatment adherence in determining disease prognosis.

Keywords: Papillon–Lefèvre Syndrome, CTSC Gene, rare disease, dermatology

CTSC Geninde Yeni Tanımlanan Homozigot c.872G>A Mutasyonu ile İlişkili Papillon-Lefèvre Sendromu: Bir Vaka Raporu

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ÖZ

Papillon-Lefèvre sendromu (PLS), CTSC genindeki patojenik varyantlara bağlı olarak gelişen, otozomal resesif kalıtılan nadir bir genodermatozdur. Hastalık; palmoplantar keratoderma ile erken başlangıçlı ve hızla ilerleyen periodontitisin birlikte görülmesiyle karakterizedir. Bu yazıda, CTSC geninde literatürde daha önce tanımlanmamış homozigot c.872G>A varyantı saptanan 21 yaşında kadın bir olgu sunulmaktadır.

Hastada çocukluk döneminden itibaren palmoplantar bölgelerde belirgin hiperkeratoz, erken diş kayıpları ve oral protez kullanımı mevcuttu. Aile öyküsünde benzer dermatolojik tabloya sahip bireylerin bulunması ve ebeveynlerin akraba olması, otozomal resesif kalıtımı desteklemektedir. Moleküler genetik analiz sonucunda tespit edilen varyant, klinik fenotip ile birlikte değerlendirilmiş ve Amerikan Tıbbi Genetik ve Genomik Koleji (ACMG) kriterlerine göre muhtemelen patojenik olarak sınıflandırılmıştır.

Hastaya sistemik retinoid tedavisi önerilmiş olsa da tedavi, hastanın isteği doğrultusunda başlatılamamıştır. Bu olgu, PLS'nin genetik çeşitliliğine katkı sunmakla birlikte, erken tanının, multidisipliner yaklaşımın ve hastanın tedavi uyumunun hastalık prognozu üzerindeki belirleyici önemini vurgulamaktadır.

Anahtar Kelimeler: Papillon–Lefèvre Sendromu, CTSC, nadir hastalık, dermatoloji

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Introduction

Papillon–Lefèvre syndrome (PLS) is a rare hereditary genodermatosis characterized by palmoplantar keratoderma (PPK) and early onset severe periodontitis. The syndrome was first described in 1924 by French physicians Papillon and Lefèvre in a brother-sister pair born to consanguineous parents, presenting with marked hyperkeratosis of the palms and soles accompanied by severe periodontitis.^{1,2}

It is an autosomal recessive genodermatosis caused by mutations in the *cathepsin C* (*CTSC*) gene, leading to thickening and erythema of the palms and soles, along with destructive periodontitis affecting both the primary and permanent dentition. Additional manifestations may include hyperhidrosis, arachnodactyly, intracranial calcifications, increased susceptibility to infections, and intellectual disabilities. Pedigree analyses further support an autosomal recessive inheritance pattern.³

The etiopathogenesis of PLS has not yet been fully elucidated. This disorder affects both sexes equally and does not demonstrate a clear racial predisposition. In addition to anatomical, microbial, and viral factors, host immune responses are thought to play a significant role in disease development.³ Early diagnosis is crucial for planning appropriate treatment strategies.⁴

PLS management generally requires a multidisciplinary therapeutic approach. Early periodontal treatment may slow the destruction of gingival tissues, thereby reducing the severity and progression of periodontitis.⁵

The dermatological manifestations of PLS are typically managed with emollients; adding salicylic acid or topical corticosteroids can enhance therapeutic efficacy. Several studies have demonstrated the effectiveness of oral retinoids, such as acitretin, etretinate, and isotretinoin, in addressing both cutaneous and dental manifestations of the condition.³

The literature highlights that early diagnosis and multidisciplinary management significantly reduce periodontal destruction and limit the progression of cutaneous lesions in PLS.⁵ However, in the case presented below, delays in both dental and dermatological treatments markedly affected the clinical course of the disease. This case underscores the influence of delayed diagnosis and treatment on disease prognosis.

Case

A 21-year-old female presented to our clinic with complaints of thickened palmoplantar skin. The patient reported that her symptoms had persisted since childhood. She experienced difficulty performing manual tasks and noted pruritus on the palms and soles. Dermatological examination revealed prominent hyperkeratosis in both hands and feet, prompting a full-body skin assessment. Oral mucosal examination revealed the presence of dental prostheses; upon removal, complete tooth loss was observed. The patient stated that she had suffered from recurrent gingivitis during childhood, had undergone various treatments, and had

subsequently lost all her teeth.

Further dermatological evaluation revealed folliculitis-like lesions and widespread secondary anetoderma-like changes attributed to chronic folliculitis in the bilateral gluteal regions (Figure 1). Family history indicated similar findings among the relatives, and it was learned that the patient's parents were consanguineous.

An incisional biopsy was performed from the plantar region, with preliminary diagnoses of palmoplantar keratoderma and psoriasis. The histopathological evaluation was consistent with keratoderma.

The patient was referred to the Department of Medical Genetics for a preliminary diagnosis of Papillon–Lefèvre syndrome. Genetic consultation revealed that the patient's mother and three maternal aunts had similar plantar hyperkeratosis, the parents were first cousins, and the maternal grandparents were from the same small village. These findings support the increased likelihood of an autosomal recessive disorder. Molecular genetic testing identified a homozygous *CTSC* variant, c.872G>A. A comprehensive review of the literature and variant databases indicated that this alteration was not previously associated with *CTSC*-related disease. Considering the patient's clinical presentation, the variant was classified as likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria. Segregation analysis was performed to prioritize symptomatic family members (Figure 2).

A definitive diagnosis of Papillon–Lefèvre syndrome was established, and systemic retinoid therapy (acitretin) was planned. However, the patient declined treatment and discontinued follow-up of her own accord. The clinical course of the patient from early childhood to adulthood is summarized (Figure 3).

Discussion and Conclusion

Papillon–Lefèvre syndrome (PLS) is a rare autosomal recessive genodermatosis caused by mutations in *CTSC*. Loss of cathepsin C enzymatic activity impairs neutrophil function and host defense, leading to early onset, rapidly progressive periodontitis and palmoplantar keratoderma.⁶

The homozygous *CTSC* c.872G>A variant identified in our patient has not been previously reported, suggesting a potential novel mutation. Concordance between clinical findings and genetic results supports the classification of this variant as likely pathogenic.

PLS typically presents in childhood as gingival infections and early tooth loss; however, delays in diagnosis are common. Early recognition is crucial to mitigate both the progression of periodontitis and severity of dermatologic manifestations.⁷

Early initiation of systemic retinoid therapy, particularly acitretin, has been shown to ameliorate palmoplantar keratoderma and reduce inflammatory destruction in periodontal tissues.⁸

In our case, the diagnosis was confirmed using a

multidisciplinary approach involving dermatology, medical genetics, and dentistry. Although systemic retinoid therapy was planned, the patient declined the treatment. This underscores that beyond pharmacologic intervention, patient education, engagement in the treatment process, and regular follow-up play essential roles in determining prognosis.

The presence of similar findings in family members and first-degree consanguinity strongly support autosomal recessive inheritance. Therefore, segregation analysis and genetic counseling for relatives are important for both

diagnostic confirmation and the assessment of future carrier risk.

In conclusion, this case demonstrates the genetic diversity and phenotypic variability of Papillon–Lefèvre syndrome. The identification of a novel *CTSC* variant contributes to the understanding of the molecular pathogenesis of the disease and genotype–phenotype correlation. Early diagnosis, multidisciplinary management strategy, and ensuring patient adherence are key elements in preventing functional and aesthetic complications associated with PLS.

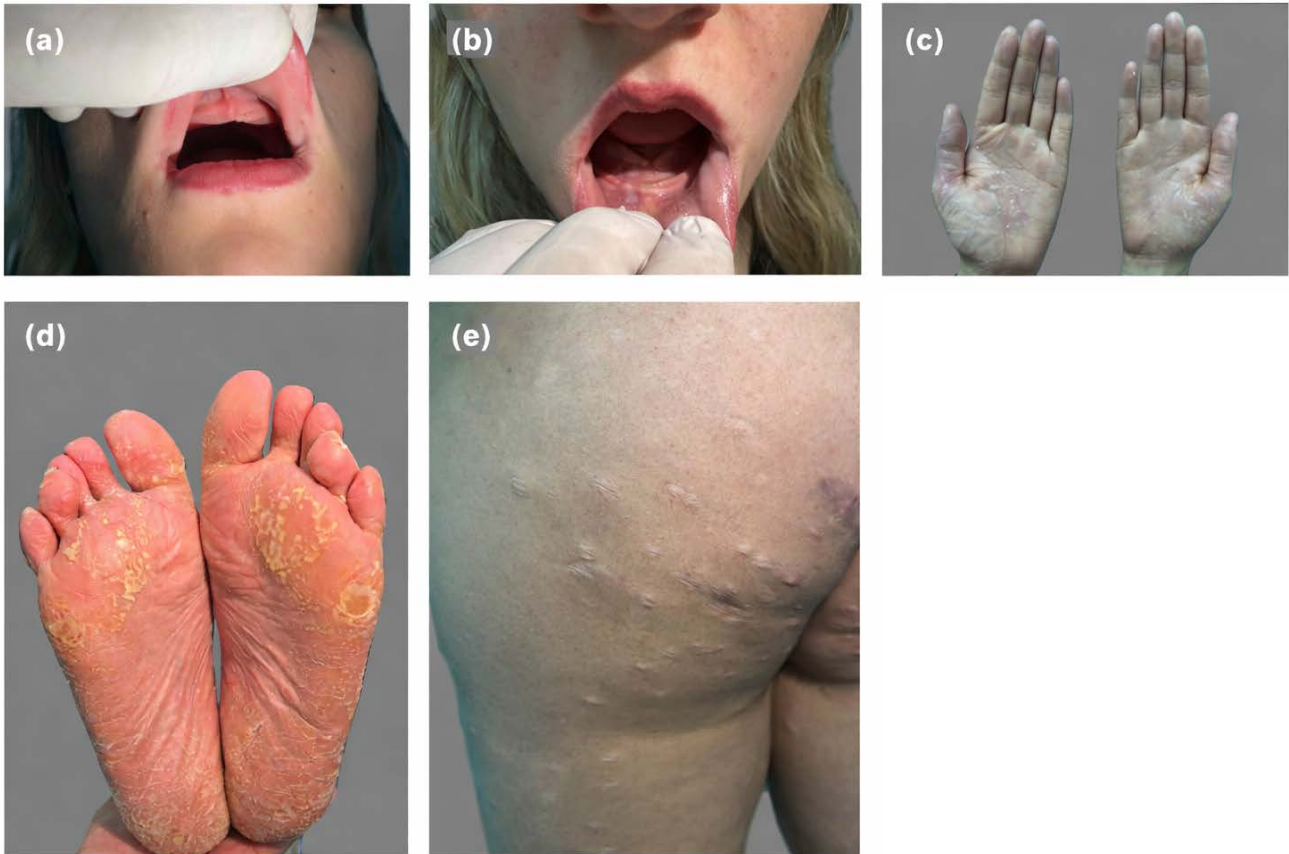


Figure 1. Clinical findings of the patient. **(a)-(b)** Complete tooth loss in both maxillary and mandibular arches. **(c)** Palmoplantar keratoderma with a transgrediens pattern on the palmar surfaces. **(d)** Focal hyperkeratotic plaques on the plantar region. **(e)** Anetoderma-like lesions secondary to folliculitis on the left gluteal area

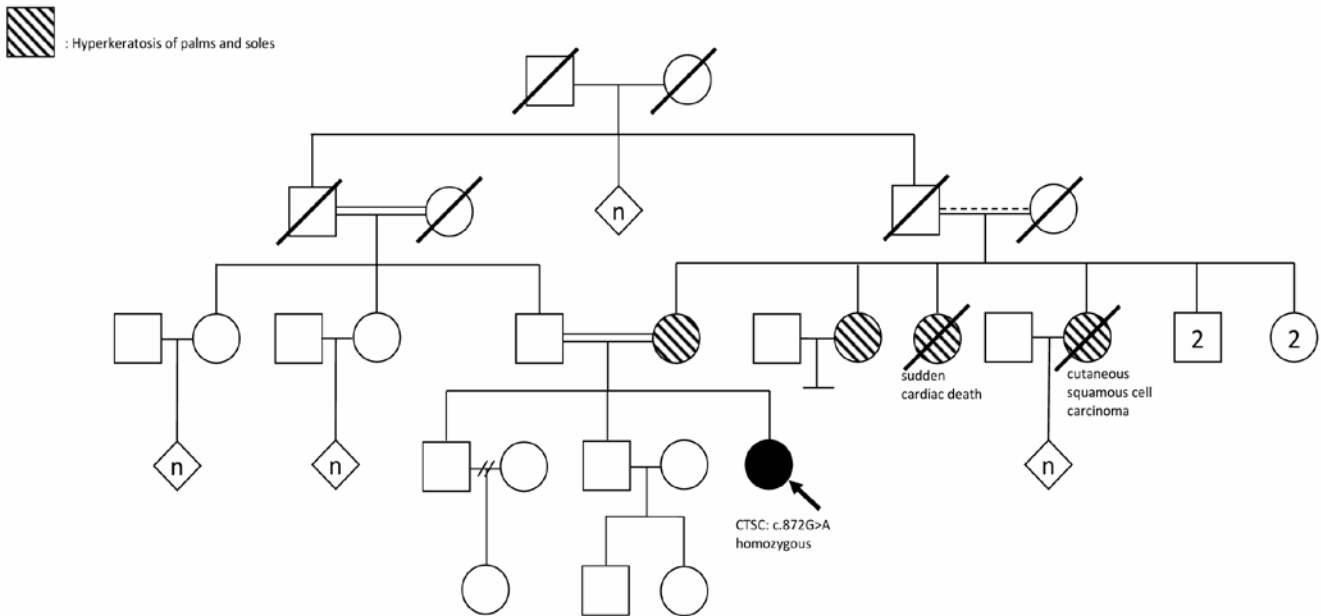


Figure 2. Segregation analysis revealed that the patient's mother and three maternal aunts exhibited similar plantar hyperkeratosis. It also demonstrated that the parents were first cousins and that the maternal grandparents originated from the same lineage.

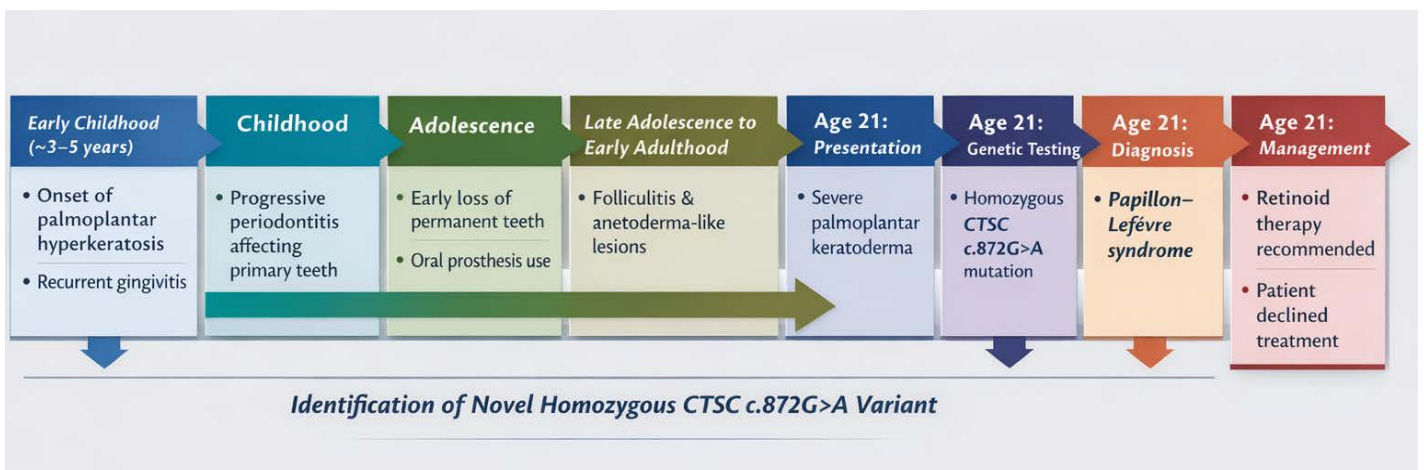


Figure 3. Timeline illustrating the chronological clinical course of Papillon-Lefèvre syndrome in the patient, from early cutaneous and periodontal manifestations to genetic confirmation of a homozygous CTSC c.872G>A variant and management planning.

Declarations

Ethical statement: This study was conducted in accordance with the principles of the Declaration of Helsinki (1964, revised 2024). Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Sivas Cumhuriyet University.

Author contributions: Ünsal AT: Concept, Design, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing, Critical Review; Güner RY: Collection and/or Processing, Analysis and/or Interpretation, Critical Review; Şimşir HS: Collection and/or Processing, Critical Review

Consent to participate: Yes

Consent for publication: Written informed consent for publication of clinical images was obtained from the patient.

Conflicts of interest statement: The authors declare that they have no conflicts of interest regarding this study.

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