Novel Compound Heterozygous Mutations in CTSC Gene in a Chinese Family with Papillon–Lefevre Syndrome

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Papillon–Lefevre syndrome (PLS) (OMIM: 245000) is a rare autosomal recessive disorder characterized by palmoplantar hyperkeratosis and early onset periodontitis, resulting in the premature loss of the deciduous and permanent teeth. PLS is caused by mutations in the cathepsin C (CTSC) gene (OMIM: 602365), which has been mapped to chromosome 11q14–q21. Genetic analysis can help early and rapid diagnosis of PLS. Here we report on a Chinese PLS pedigree with two affected siblings. We have identified two novel compound heterozygous mutations c.763T>C (p.C255R) and c.1015C>A (p.R339S) in the CTSC gene. The two mutations expand the spectrum of CTSC mutations in PLS. (Ann Dermatol 33(4) 369 ~ 372, 2021)

-Keywords-
Cathepsin C, Palmoplantar keratoderma, Papillon–Lefevre syndrome, Periodontitis

INTRODUCTION

Papillon–Lefevre syndrome (PLS) (OMIM: 245000) is a rare autosomal recessive disorder characterized by palmoplantar hyperkeratosis and progressive periodontitis, which consequently results in the premature loss of the deciduous and permanent dentitions. Palmoplantar keratosis, varying from mild psoriasiform scaly skin to overt hyperkeratosis, typically develops within the first three years of life. The prevalence of PLS is reported to be 1 to 4 cases per million in the general population with no gender preference. The disease is caused by mutations in the cathepsin C (CTSC) gene which located on chromosome 11q14–q21. CTSC is a lysosomal protease and has an essential role in antibacterial effects and stimulation of cytokines through the activation of serine proteases within polymorphonuclear cells and macrophages. Despite existing functional abnormalities in neutrophils and natural killer cells of patients with PLS, the systemic immunodeficiency is relatively mild in PLS. Here we report on a Chinese PLS pedigree with two affected siblings and the identification of two novel mutations in the CTSC gene.

CASE REPORT

Patient 1

A 9-year-old boy presented with hyperkeratosis on palms and soles at four months after birth, the skin lesions had gradually spread to the knees and elbows. Physical examination revealed bilateral, symmetrical and demarcated hyperkeratotic plaques and fissures on the palms and soles. There were symmetrical psoriasiform lesions on his knees and elbows (Fig. 1A, B). The boy also complained of periodontal problems. Dental history indicated the boy had severe periodontal disease (Fig. 1C), deciduous teeth started to lose since the age of four, and the disease led to all deciduous teeth loss before 9-year-old. Intraoral examination revealed permanent teeth erupted prematurely and most of them were loose, and the gingiva was edematous.
Fig. 1. (A) Psoriasiform lesions on knees of patient 1. (B) Hyperkeratosis on palms and soles of patient 1. (C) Dental finding of patient 1. (D) Hyperkeratosis on soles of patient 2. (E) Hyperkeratosis on palms of patient 2.

Fig. 2. Genetic analysis revealed compound heterozygous mutations including two missense changes in the two patients. Their father and mother were heterozygous for c.763T>C and c.1015C>A, respectively. Both of them were carriers of CTSC gene mutation. (A) c.763T>C in exon 6 (p.C255R). (B) c.1015C>A in exon 7 (p.R339S).

Genomic DNA was isolated from peripheral blood of the two patients and their unaffected parents, and whole-exome sequencing was performed, then all mutations had been verified by direct Sanger sequencing. Genetic analysis discovered novel compound heterozygous missense mutations in the siblings: c.763T>C (p.C255R) in exon 6 (Fig. 2A) and c.1015C>A (p.R339S) in exon 7 (Fig. 2B). Their father and mother were heterozygous for c.763T>C and c.1015C>A, respectively. Both of them were carriers of CTSC gene mutation. We also used the SIFT and Polyphen software to predict the phenotypic effects caused by p.C255R and p.R339S amino acid mutations, which were probably damaging, suggesting that the above heterozygous mutation might affect the normal function of CTSC protein.

Based on the clinical manifestations and genetic analysis, the diagnosis of PLS was made. The two patients were advised to maintain their oral hygiene. Oral acitretin was

with formation of periodontal pockets. Dental X-ray (orthopantomogram view) found alveolar bones resorption and affected teeth lacked of osseous support.

**Patient 2**

A 2-year-old boy, the younger brother of the first patient, was also referred to our institution for the similar symptoms as his brother (Fig. 1D, E). Palmoplantar hyperkeratosis started at the age of 3 months. At the present stage, the boy had no obvious periodontal problems or loss of deciduous teeth. His medical history showed he had no serious infectious disease; his unaffected parents were not intermarriage.

**Genetic analysis**

Genomic DNA was isolated from peripheral blood of the
prescribed at a dose of 10 mg/day to the elder brother, his skin lesions showed a marked improvement after 1 month. The younger brother was only given topical emollients due to his young age.

We received the patient’s consent form about publishing all photographic materials.

**DISCUSSION**

Nowadays, There were 77 different mutations in the CTSC gene have been reported worldwide (Human Gene Mutation Database), most of them are located in exons 5 to 7, which encode the heavy chain region of the cathepsin C protein and the heavy chain region is important for enzyme activity. What we have reported the p.C255R and p.R339S mutations in the two patients are also located in this region, and we used bioinformatics analysis to predict phenotypic effects that were probably damaging. These mutations led to changes in peptidase C1A and papain C-terminal functional domain, which were supposed to be highly conserved, so we suggested these changes might damage the protein’s function and the enzyme activity significantly.

In the past, most commonly, PLS patients were reported to be born to consanguineous parents, correlating with the described mutations are homozygous. However, in our cases, the two patients are belonging to compound heterozygous missense mutations, their unaffected parents were non-consanguineous. In the present cases, the two novel mutations led to typical dental and skin lesions, while the siblings did not have recurrent infections. The mutations c.763T>C (p.C255R) and c.1015C>A (p.R339S) did not show more severe phenotypes than other mutations in the CTSC gene.

It is reported that mutations in the CTSC gene can lead to three closely related conditions, such as PLS, Haim-Munk syndrome and prepubertal periodontitis. Interestingly, Haim-Munk syndrome is characterized by the presence of arachnodactyly, acroosteolysis, and onychogryphosis in addition to palmoquantal keratoderma and periodontitis, while prepubertal periodontitis is usually without skin manifestations. Phenotypic variants of the CTSC mutations may be affected by other genetic or environmental factors. Further gene mutation investigations are necessary to better clarify the relationship between the genotypes and phenotypes of patients with PLS.

In conclusion, we revealed two novel compound heterozygous mutations c.763T>C (p.C255R) and c.1015C>A (p.R339S). Although the latter mutation occurred in the same location as the identified pathogenic mutation, it had different amino acid missense mutation. The two mutations expand the spectrum of CTSC mutations in PLS.

**CONFLICTS OF INTEREST**

The authors have nothing to disclose.

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