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SHORT COMMUNICATION

A novel seven-base deletion of the *CTSC* gene identified in a Hungarian family with Papillon-Lefèvre syndrome

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Abstract Papillon-Lefévre syndrome (PLS; OMIM 24500 0) is a rare autosomal recessive condition characterized by symmetrical palmoplantar hyperkeratosis and periodontal inflammation, causing loss of both the deciduous and permanent teeth. PLS develops due to mutations in the cathepsin C gene, *CTSC*. Recently we have identified a Hungarian PLS family with two affected siblings. Direct sequencing of the coding regions of the *CTSC* gene revealed a novel seven-base deletion leading to frameshift and early stop codon in the fourth exon of the *CTSC* gene (c.681delCATACAT, p.T188fsX199). The affected family members carried the mutation in homozygous form, while the clinically unaffected family members carried the mutation in heterozygous form. The unrelated controls carried only the wild type sequence. In this paper we report a novel homozygous deletion of seven bases on the *CTSC* gene leading to the development of PLS. Since consanguineous marriage was unknown in the investigated family, the presence of the homozygous seven-base deletion of the *CTSC* gene may suggest that the parents are close relatives.

Keywords Papillon-Lefévre syndrome · Palmoplantar hyperkeratosis · Periodontal inflammation · Cathepsin C gene · Deletion

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Introduction

Papillon-Lefévre syndrome (PLS; OMIM 245000) is a rare autosomal recessive disease, manifesting with symmetrical palmoplantar keratoderma and periodontitis [5]. The keratoderma in PLS may already be present in the first 3 months of life, but in general the palmoplantar hyperkeratosis and the severe periodontitis present simultaneously between 1 and 4 years of age [1]. Besides these symptoms, mild mental retardation, intracranial calcifications as well as hyperhidrosis may occur [1]. The occurence of the disease is 1–4 cases per million; so far approximately 300 cases have been reported worldwide [3]. PLS is the consequence of mutations located in the cathepsin C (*CTSC*) gene. Here we report on a Hungarian PLS pedigree with two affected siblings and the identification of a novel mutation in the *CTSC* gene.

Materials and methods

Patients

A 11-year-old Hungarian girl (Patient I) was referred to our out-patient clinic with a common phenotype of PLS. The

patient was presented with the typical skin symptoms of PLS, complicated with palmoplantar eruption. On referral sharply circumscribed erythema with minimal hyperkeratosis and shedding was seen on both palms (Fig. 1a). The erythema on the plantar surfaces was minimal, however hyperkeratosis with deep fissures dominated (Fig. 1b). These abnormalities first appeared at her age of 19 months. At the age of 4 years, the dermatological findings were also associated with the presence of severe periodontitis, leading to the loss of all deciduous teeth. The other patient (Patient II) was a 2-year-old Hungarian girl, the younger sister of Patient I. She was also referred to our department for having similar symptoms as her older sibling. Palmoplantar eruptions started at the age of 10 months. On referral, minimal erythema was seen on the distal fingertips (Fig. 1c) and erythema with minimal hyperkeratosis was present on the soles of the feet (Fig. 1d). Periodontal inflammation of the deciduous dentition (Fig. 1e) presented together with the dermatologic lesions, although her symptoms were milder compared to that of her older sibling. The symptomless parents reported on a 16-year-old sister of the affected daughters, who has no symptoms (Fig. 1f).

Genetic investigations

Blood samples were taken from the patients and from their clinically unaffected family members as well as from unrelated controls ($n = 130$) for genetic investigation. Genomic DNA has been isolated by a BioRobot EZ1 DSP Workstation (Qiagen; Godollo, Hungary). The coding regions of the *CTSC* gene and the flanking introns were amplified and sequenced (primers were used as displayed on the UCSC Genome Browser www.genome.ucsc.edu).

Results

Direct sequencing of the coding regions and the flanking introns of the *CTSC* gene revealed a novel seven-base deletion in the fourth exon (c.681delCATACAT, p.T188fsX199). This deletion causes frameshift and leads to the development of a premature termination codon (TGA) 32 bases downstream of the mutation. The patients carried the mutation in homozygous form (Fig. 2a), while the unaffected family members carried the same mutation in heterozygous form (Fig. 2b). The unrelated controls carried the wild type sequence (Fig. 2c).

Discussion

The *CTSC* gene encodes cathepsin C, which is a lysosomal cysteine protease responsible for removing dipeptides from the terminus of protein substrates as well as activating many neutrophil serine proteinases. Up to now, approximately 60

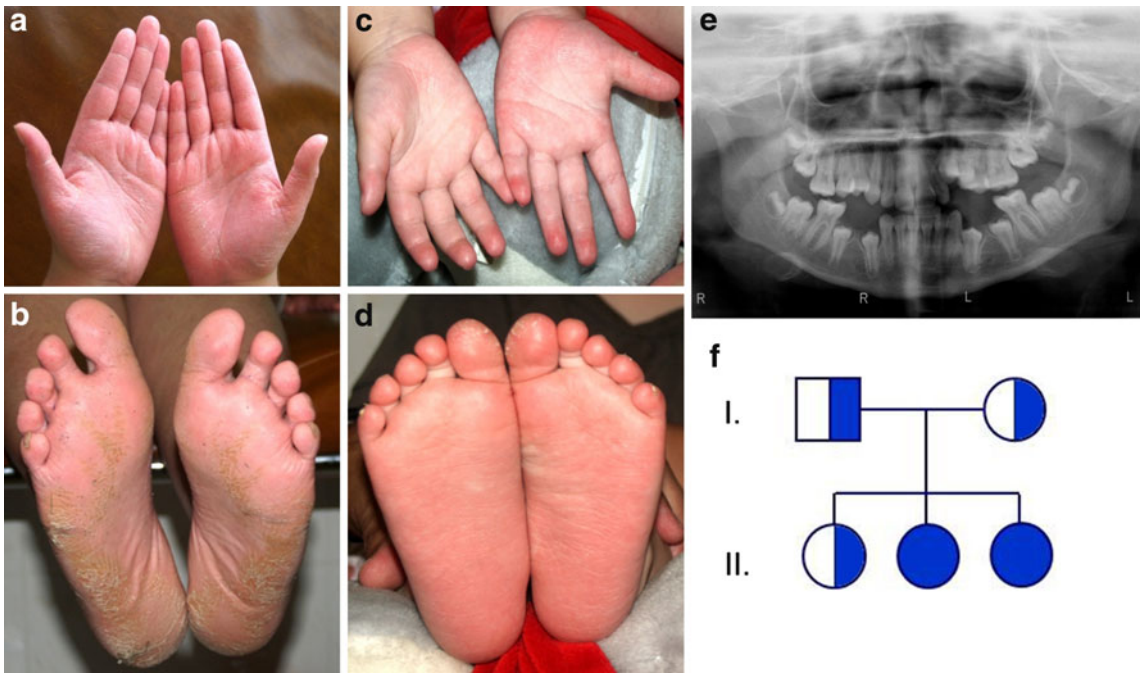

Fig. 1 The pedigree and the skin symptoms of the affected siblings. Hyperkeratosis of the palms (**a**) and the soles (**b**) in the case of Patient I. Similar symptoms of the palms (**c**) and soles (**d**) in the case of Patient II. X-ray picture of Patient II (**e**). The investigated Hungarian BSS pedigree spanning two generations and containing two clinically affected and three clinically unaffected family members (**f**)

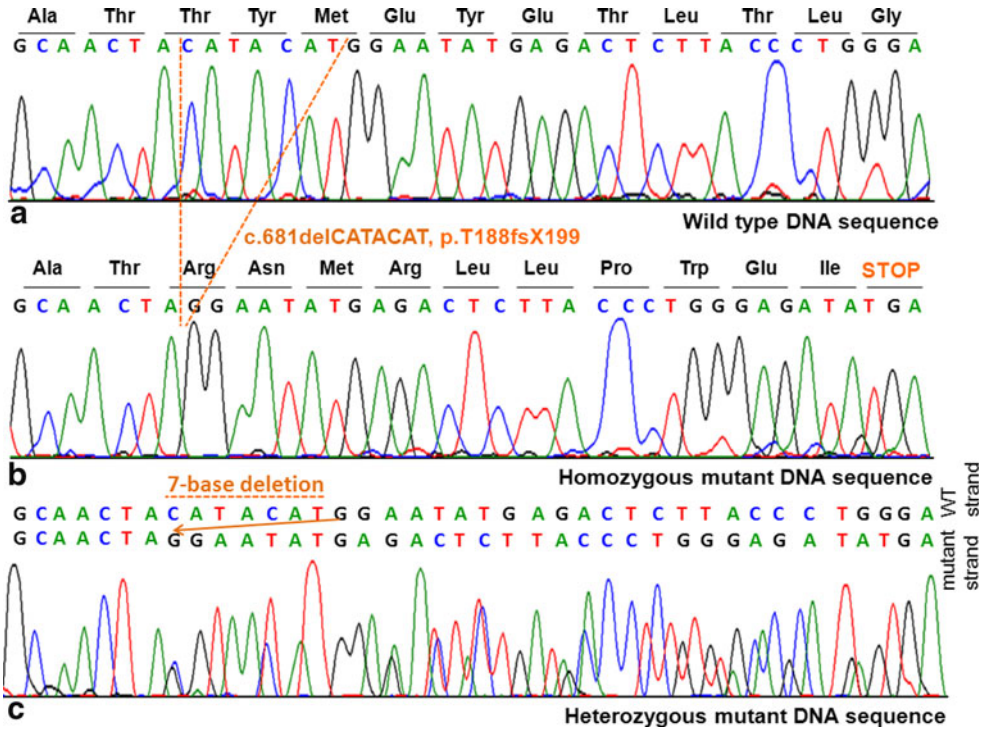

Fig. 2 Identification of a novel mutation of the *CTSC* gene. Direct sequencing revealed a seven-base deletion (c.681delCATACAT, p.T188fsX199) in the fourth exon of the *CTSC* gene. The affected family members carried the deletion in homozygous form (Fig. 2a), while the unaffected family members carried the same deletion in heterozygous form (Fig. 2b). The unrelated controls ($n = 130$) carried the wild type sequence (Fig. 2c)

different mutations have been reported worldwide on the *CTSC* gene [6]. In most of the reported PLS patients, *CTSC* mutations were present in a homozygous form and were the consequences of consanguinity within the family. Functional studies proved that the detected mutations of the *CTSC* gene are loss-of-function mutations, which led to the inactivation of the encoded cysteine protease causing disregulation of the immune response [4]. Periodontal disease and the increased susceptibility to infections have been attributed to impaired neutrophil and T and B cell functions [1, 2].

Here we report on a Hungarian PLS pedigree with two clinically affected siblings. We performed the mutational screening of the *CTSC* gene using direct sequencing and identified a novel, homozygous, seven-base deletion (c.681delCATACAT, p.T188fsX199) in the fourth exon leading to frameshift and premature termination codon at the amino acid position 199. Due to these changes the translated mutant CTSC protein is highly truncated and forms a polypeptide chain of 199 amino acid residues instead of the full length protein with 463 amino acid residues. We hypothesize that this enormous truncation of the mutant CTSC protein may lead to its dysfunction and thus to the development of PLS. The fact that the affected siblings carried the mutation in a homozygous form and the clinically unaffected parents and sibling carried it in a heterozygous form raise the possibility of consanguinity within the affected family. However, the investigated Hungarian pedigree is not aware of any consanguineous marriage in the family, the results may suggest that the parents are somehow close relatives.

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Conflict of interest The authors declare that they have no conflict of interest.

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