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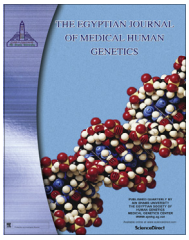

CASE REPORT

A novel nonsense mutation in cathepsin C gene in an Egyptian patient presenting with Papillon–Lefèvre syndrome

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Abstract *Background:* Cathepsin C gene (CTSC) (MIM#602365) is a lysosomal cysteine proteinase coding gene which encodes for CTSC protein that plays a major role in the activation of granule serine proteases, particularly leukocyte elastase and granzymes A and B. This activity was proposed to play a role in epithelial differentiation and desquamation. Mutations that cause Disruption in the CTSC expression or function will result in loss of immunological response such as defects of phagocytic function and deregulation of localized polymorphonuclears response with subsequent clinical manifestation.

Aim: The aim of this study is to detect the mutation in CTSC gene expected to be the cause of Papillon Lefèvre syndrome (PLS) in an Egyptian patient clinically diagnosed as PLS and to characterize the clinical features.

Patient and methods: A 5 year and 3 month old girl from the outpatient's Oro-Dental Genetics clinic – National Research Center presented with the typical clinical findings of Papillon Lefevre syndrome. Genomic DNA was extracted from peripheral blood samples of the patient, her parents and 20 healthy Egyptian controls using standard procedures. All exons of the CTSC gene were amplified by PCR. Sequence analysis of the patient, her parents and controls was performed for mutation detection.

Results: Mutation analysis of the CTSC gene in our patient revealed a novel homozygous nonsense mutation in exon 5 (W237X). Her parents revealed the presence of the same mutation in a heterozygous state. The 20 controls showed only the wild type sequence of all exons (no mutation).

Conclusion: This study reported a novel nonsense mutation in the CTSC gene in an Egyptian patient. This novel nonsense mutation is predicted to produce truncated dipeptidyl-peptidase1 causing PLS phenotype in this patient.

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1. Introduction

Papillon Lefèvre syndrome (PLS) is an autosomal recessive disorder characterized by aggressive periodontitis and palmoplantar hyperkeratosis [1]. It has a world-wide prevalence of 1–4 cases per million in the general population and is often related with consanguinity [2]. Dermatological disorders initiate with erythema and after about 6 months, they progress to hyperkeratosis of soles, palms, knees, and elbows. The major feature of Papillon Lefevre syndrome is severe periodontitis. Patients typically report two episodes of aggressive periodontitis: the first one around three years of age, leading to the loss of primary teeth [3], the second around fifteen years of age, resulting in the loss of permanent teeth [4].

The development and eruption of the deciduous teeth proceed normally, at expected ages and with normal sequence, with the teeth being of normal form and structure, but their eruption is associated with gingival inflammation and subsequent rapid destruction of the periodontium. The resulting periodontitis is usually unresponsive to traditional periodontal treatment modalities and the primary dentition is usually exfoliated prematurely by the age of 4 years. After exfoliation, the inflammation subsides and the gingiva appears healthy. However, with the eruption of the permanent dentition, the process of gingivitis and periodontitis is usually repeated and there is subsequent premature exfoliation of the permanent teeth, although the third molars are sometimes spared, where most of the permanent teeth are lost by the age of 15 and 17 years, often leaving the jaws atrophied. The tooth loss pattern often mimics the eruption pattern [5]. Severe resorption of the alveolar bone gives the teeth the "floating in air" appearance on radiographs. However, others have found variable penetrance and less severe periodontal disease [4,6–10].

In addition to these symptoms, recurrent skin infections, liver abscesses, mild mental retardation, intracranial calcifications, and hyperhidrosis have been reported [11].

The Cathepsin C gene (CTSC) is expressed in epithelial regions commonly affected by PLS such as palms, soles, knees and gingiva [12]. The loss of CTSC function and subsequent inactivity of neutrophil serine proteinases [13,14] as well as reduced neutrophil response to *staphylococcus* spp. and *Actinobacillus actinomycetemcomitans* lead to the severe periodontal tissue destruction [15].

The CTSC gene maps to chromosome 11q14.2, spans 4.7 kb and has seven exons and six introns [16–18]. Mutations in both alleles of CTSC gene have been reported as responsible for Papillion Lefevre Syndrome (PLS; OMIM 245000) [19,20] as well as similar conditions such as Haim–Munk Syndrome (HMS, OMIM 245010), and juvenile periodontitis (AP1, OMIM 170650).

In 1999, the first eight mutations of the CTSC gene were identified in 8 cases from consanguineous PLS parents [20]. Since 1999, several reports have described mutations in the CTSC gene in different PLS cases from around the world [21]. CTSC mutations have also been reported in patients with Haim–Munk syndrome (HMS, OMIM 245010) and in aggressive periodontitis (AP1, OMIM 170650), [22–24]. To date, a total of 75 mutations have been reported for the CTSC gene. The majority of the mutations (97%) were reported in PLS cases, while only a few mutations (3%) were reported in HMS or AP1 cases. Most mutations are missense (53%), nonsense (23%), or frameshift (17%); however, in-frame deletions, one splicing variant, and one 5′ untranslated region (UTR) mutation have also been reported. The majority of the mutations are located in exons 5–7, which encodes the heavy chain of the cathepsin C protein, suggesting that tetramerization is important for cathepsin C enzymatic activity [21]. Note that some mutations were detected in two different disease entities: c.1040A > G p.Tyr347Cys was reported for AP1 and also for classic PLS families [20,22–24], c.145C > T p.Gln49X and c.857A > G p.Gln286Arg mutations were reported for HMS and PLS pedigrees [25,26]. Therefore, PLS, HMS, and AP1 are not different entities; they represent the phenotypic spectrum of a single disease [27].

2. Patient and methods

2.1. Patient's clinical data

A 5 year and 3 month old girl came to the outpatient's Oro-Dental Genetics clinic – National Research Center and presented with the typical clinical findings of Papillon Lefevre syndrome as described by Papillon & Lefevre in 1924 [1]. Her chief complaint was early loss of her anterior teeth by the age of 3 yrs. The girl was born out of a consanguineous marriage, with two unaffected siblings. Intraoral examination revealed generalized aggressive periodontitis with premature loss of the four primary central incisors. Dermatological examination revealed mild localized keratotic plaques on both the palms and soles which according to her mother, responded very well to the retinoids therapy, which started seven months ago (Fig. 1a and b). The gingiva was edematous with loss of stippling. Grade III mobility was noticed in the upper canines which explains the discomfort described by the patient while eating. Pocket probing depths of the remaining teeth were on average of 4–6 mm (Fig. 1c and d).

2.2. Molecular studies

Our study has been carried out in accordance with The Code of Ethics of the World Medical Association for experiments involving humans. Written informed consent was obtained from the patient's parents and 20 healthy Egyptian controls, according to Medical Ethics Committee of the National Research Center.

Genomic DNA was extracted from peripheral blood samples using standard procedures. All exons of the CTSC gene were amplified by PCR using intron-specific primers [20], except for the developed primer pairs for exons 1 and the 5′ half of exon 7 (Table 1)]. PCR was performed in a final volume of 25 µl containing ~100 ng genomic DNA, MgCl 2 (1.5 m M), dNTP mixture (0.2 m M), Taq DNA polymerase (2 U/µl), and 10 µM of each primer (MWG-BIOtech, Ebersberg, Germany).

Conditions of PCR comprised 1 cycle of denaturation at 95 °C for 2 min followed by 35 cycles of 30 s at 94 °C, 30 s at annealing temperature (Tm primer), and 1 min extension at 72 °C followed by a final extension at 72 °C for 7 min in a thermal cycler (Agilent Technologies Sure Cycler 8800). 5 µl aliquots of the PCR products were analyzed by 2% agarose gel electrophoresis.

PCR products were purified using the QIA Quick PCR Purification kit (Qiagene) followed by bidirectional sequencing using the ABI Prism Big Dye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems) and the sequencing reaction products were separated on an ABI Prism 310 Genetic Analyzer (Applied Biosystems). Alignment of sequenced results used NCBI genomic sequence NG_008365.1 and reference cDNA sequence NM_000348.3 for result interpretation.

3. Results

Mutation analysis of the CTSC gene in our patient revealed a homozygous nonsense mutation in exon 5 at the nucleotide position c.711 (TGG was replaced by TAG, c.711G > A) resulting in a premature stop codon instead of tryptophan at codon 237 (p.W237X) (Fig. 2A). Sequence analysis of CTSC gene for her parents revealed the presence of the same mutation (W237X) in a heterozygous state (Fig. 2B). Her mother carries the heterozygous form of the T153I variant (resulting in the substitution of Isoleucine (ATA) by Threonine (ACA) at codon 153) and her father carries the wild type form. On the other hand, the 20 control individuals showed only the wild type sequence of exon 5 (no mutation) (Fig. 2C). With respect to T153I variant in the control group 2 carried the homozygous form, 2 were heterozygous and the rest were wild type. The patient also disclosed the wild type variant T15 I in exon 3.

4. Discussion

CTSC gene (MIM#602365) also named dipeptidyl-peptidase I (DPPI) is a lysosomal cysteine proteinase, which plays an important role in intracellular degradation of proteins and also

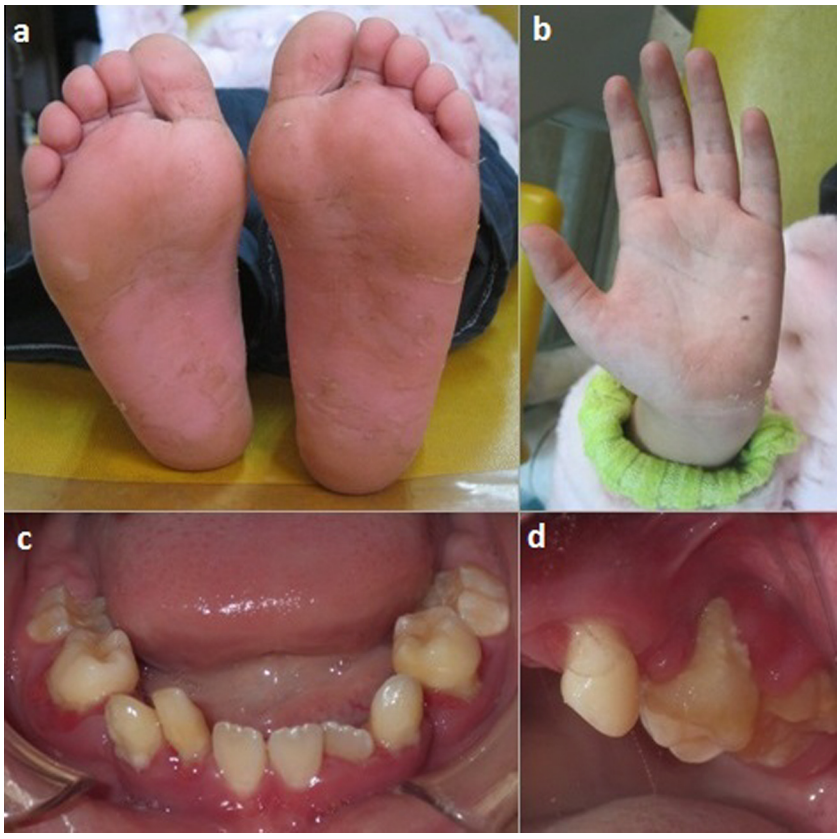

Figure 1 (a and b) showing palmoplantar hyperkeratosis, (c and d) showing severe periodontitis related to primary teeth, the gingiva is edematous with loss of stippling.

Table 1 Sequence of forward and reverse primers of exons1–7 of CTSC gene.

Exon no.	Sequence of forward primer	Sequence of reverse primer
1	5′-TCTTCACCTCTTTTCTCAGC-3′	5′-GGTCCCCGAATCCAGTCAAG-3′
2	5′-GACTGTGCTCAAACTGGGTAG-3′	5′-CTACTAATCAGAAGAGGTTTCAG-3′
3	5′-GGGGCACATTTACTGTGAATG-3′	5′-CGTATGTCTCATTTGTAGCAAC-3′
4	5′-GTACCACTTTCCACTTAGGCA-3′	5′-GGAGGATGGTATTCAGCATTC-3′
5	5′-CCTAGCTAGTCTGGTAGCTG-3′	5′-GTATCCCCGAAATCCATCACA-3′
6	5′-CTCTGTGAGGCTTCAGATGTC-3′	5′-CAACAGCCAGCTGCACACAG-3′
7a	5′-CGGCTTCCTGGTAATTCTTC-3′	5′-GTAGTGGAGGAAGTCATCATATAC-3′
7b	5′-CAATGAAGCCCTGATCAAGC-3′	5′-CTTCTGAGATTGCTGCTGAAAG-3′

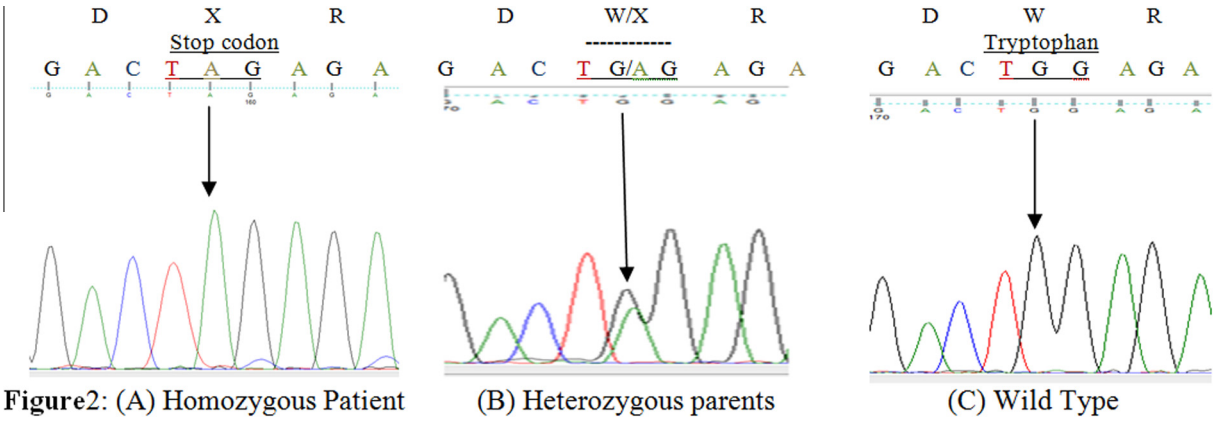

Figure 2 Sequence chromatogram of the detected mutation: (A) sequence of exon 5 of CTSC gene at codon 237 showing W237X homozygous mutation (patient), (B) codon 237 showing W237X heterozygous mutation (parents), (C) the wild type of codon 237(controls).

processes and activates many serine proteinases in immune/inflammatory cells [28]. The CTSC gene locus has been mapped to a 2.8 cm interval on chromosome 11q14, flanked by D11S4197 and D11S931 [19,29,30].

Up till now, approximately 75 different mutations have been reported worldwide on the CTSC gene [21]. Of these mutations, 85% were present only in homozygous form in PLS patients, while 15% were detected in a compound heterozygous state. Among the homozygous mutations, 50% were missense, 25% nonsense, 23% frameshift mutations, and 2% were other types of mutations [21].

All CTSC mutations have either a dramatic impact on the coding region (nonsense, frameshift, or splicing mutations) or have altered evolutionarily conserved amino acids (missense) [8–10,31].

Nonsense mutations occur in all coding regions of the gene; however, the majority is located in exons 5–7, encoding the heavy-chain region of the cathepsin C protein which is thought to be important for enzyme activity [32].

Genetic testing of the current case revealed the presence of a novel homozygous nonsense mutation in exon 5 (c.711G > A), leading to the substitution of Tryptophan amino acid to a stop codon at codon 237 (p.W237X) resulting in the truncation of the CTSC encoded enzyme dipeptidyl-peptidase 1 with the introduction of premature stop codon.

The nucleotide change reported here (W237X) fulfilled the criteria of a mutation [33] as it was not present in the 20 controls and results in the truncation of the CTSC encoded enzyme dipeptidyl-peptidase1 with the introduction of premature stop codon.

In addition to mutations of the CTSC gene, it is important to note that the c.458C > T p.Thr153Ile missense variant is a common polymorphisms for this gene and corresponds to variant rs217086, occurs at a residue that is conserved in mammals and is located in the portion of the propeptide that is cleaved upon activation [34]. The Thr153Ile polymorphism has been indentified in several PLS families, but does not have a causative role in the development of PLS [13,27,35,36].

Thr153Ile polymorphism occurs at a residue conserved between humans and dogs and is in the portion of the pro-region that is normally cleaved out upon activation. Given that the T153I polymorphism occurs within 10 amino acids of the N-terminal cleavage site, it is attractive to hypothesize that the mutation interferes with or prevents this normal processing.

Comparison of clinical features in affected families with the same mutation strongly confirms that identical mutations of the CTSC gene can give rise to multiple different phenotypes, making genotype–phenotype correlations difficult [37].

Four mutations were previously described in Egyptian patients with PLS (Table 2). These mutations are c.IVS3-1G > A, R210X, Q252L and R339C (20, 22, 38, 39 and unpublished data). With respect to the ethnicity of these mutations and the fact of high consanguineous marriage rate among Egyptian population which represent more than 30% [40] these mutations are mostly attributed to a founder gene effect due to the neighborhood of the Arab countries, the British occupation to Martinique and Egypt and the Turkish occupation to Egypt.

Table 2 Summary of studies reporting mutations in CTSC gene in Egyptian patients and their repetition in other populations.

Site	Mutation	Amino acid	Type of mutation	Ethnicity	Ref.
Intron 3	c.485-1G > A	c.IVS3-1G > A	Splice site	Egyptian, Jordanian	[20,38] and unpublished data
Exon 4	c.628C > T	R210X	Nonsense	Egyptian, Lebanese, Algeria	[20,39] and unpublished data
Exon 5	c.711 G > A	W237X*	Nonsense	Egyptian	The present study
	c.755 A > T	Q252L	Missense	Egyptian	[20]
Exon 7	c.1015 C > T	R339C	Missense	Egyptian, Martinique, Turkish	[20,22,39] and unpublished data

* Novel mutation.

In conclusion, we have detected a novel nonsense homozygous mutation in the CTSC gene, extending the spectrum of mutations in the CTSC gene.

Conflict of interest

Authors of manuscript declare no conflict of interest.

Acknowledgements

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