Cathepsin-C (CTSC) Gene Mutations in Papillon-Lefevre Syndrome in India.

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Abstract

Background: Papillon Lefevre Syndrome (PLS) is a rare autosomal recessive disorder characterized by severe early onset periodontopathia and palmoplantar hyperkeratosis leading to premature loss of both primary and permanent dentition. PLS is caused by mutations in cathepsin C (CTSC) gene. The prevalence being 1-4 per million individuals with a carrier rate of 2 to 4 per million with no sex prediction and no racial predominance, onethird of all reported cases having consanguineous parents. A major gene locus for PLS has been mapped on chromosome 11q14. Correlation of physical and genetic maps of this interval indicate it includes at least 40 ESTs and six known genes including the lysosomal protease CTSC gene.

Methods: Peripheral blood samples were obtained from three families with a total of 14 members of which 7 with PLS and others as ethnically matched controls were studied. DNA was extracted and all the 7 exons of the CTSC gene amplified by the polymerase chain reaction (PCR) using specific primers. All the PCR amplicons were subjected to automated DNA sequencing for mutations analysis.

Results: The mutation spectrum shows that, in exon 2, 5 and 6 only missense mutations and in exon 3 only frame shift insertion were observed. Hence the total number of mutations observed in this study are 6. Out of this 5 are missense mutations and 1 is a frame shift insertion.

Conclusions: This study describes a novel mutation of the cathepsin C gene in an Indian population with Papillon-Lefèvre syndrome.

Introduction

The Papillon-Lefevre syndrome (PLS) is a rare genodermatosis of autosomal recessive inheritance manifesting as palmar plantar hyperkeratosis with early onset periodontitis[1]. It was first described by two French physicians, Papillon and Lefevre, in 1924. It has a prevalence of 1–4 cases per million persons and both males and females are equally affected with no racial predominance[2], [3]. The disorder is characterized by diffuse palmoplantar keratoderma and premature loss of both deciduous and permanent teeth. The palmoplantar keratoderma typically has its onset between the ages one and four years [4]. The sharply demarcated erythematous keratotic plaques may occur focally, but usually involve the entire surface of palms and soles resulting in foul-smelling odor[5]. Well-demarcated psoriasiform plaques occur on elbows and knees[6]. This may worsen in winter and be associated with painful fissures.

The second major feature of PLS is severe periodontitis, which starts at the age of three or four years[7]. The development and eruption of deciduous teeth proceeds normally, but their eruption is associated with gingival inflammation and subsequent rapid destruction of the periodontium. The resulting periodontitis characteristically is unresponsive to traditional periodontal treatment modalities and the primary dentition is usually exfoliated prematurely by the age four years. After exfoliation, the inflammation subsides and gingiva appears healthy. However, with 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[8], [9] .

Although the cause of PLS is not well understood, it has been reported that loss of the functional mutation effecting both the alleles of cathepsin C gene, located on chromosome 11q14.1-q14.3 is associated with PLS. [10],[11] The cathepsin C (CTSC) gene encodes a cystine lysosomal protease, also known as dipeptidyl peptidase I, which functions to remove dipeptides from the amino terminus of protein substrate. It also has endopeptidase activity. CTSC gene is expressed in the epithelial region commonly affected by PLS such as palms, soles, knees, and keratinized oral gingiva. It is also expressed at high levels in various immune cells including polymorphonuclear leukocytes, macrophages, and their precursors. Several mutations have been reported in the cathepsin C gene in individuals from diverse ethnic groups.

An increased prevalence of parental consanguinity has been reported in PLS patients [2]. All PLS patients are homozygous for the same CTSC gene mutation inherited from a common ancestor. It would be pertinent to mention that there are reports of at least six cases of late onset variation of PLS without underlying CTSC gene mutation [12].

Materials And Methods

Patient selection and clinical sample collection

In this study three families, total 14 (PLS1 to PLS14) individuals were recruited and analyzed for mutations in CTSC gene. Out of 14 the individuals PLS1, PLS2, PLS3, PLS7, PLS8, PLS12 and PLS13 were exhibiting extreme clinical manifestation of PLS. Rest of the PLS individuals (4, 5, 6, 9, 10, 11 and 14) were family members not exhibiting any clinical features of PLS. PLS1 – PLS5 belong to family 1 which was reported from SDM College of Dental Sciences and hospital, Dharwad, India. PLS6- PLS8 belong to family 2 and PLS 10–14 belong to family 3, both the families were reported in S. S Dental College, Davangere.

The pedigree investigations of the affected families showed similar clinical features in the siblings. Further the parents of the patients in all the families had consanguineous marriage. After obtaining informed consent in vernacular from all the members of the affected families, 3 ml of peripheral blood samples were collected in EDTA coated vacutainer (BD Biosciences). The collected samples were coded and transported to research laboratory at 4 °C.

DNA Isolation

The genomic DNA was extracted (Bangalore Genei, Whole Blood DNA Extraction Kit Cat. No.105563) from all the collected blood samples as per the instructions of the manufacturer. The DNA was quantified using Bio Photometer (Eppendorf). This DNA was used as template for Polymerase Chain Reaction (PCR) amplification of all the exons of CTSC gene for mutation detection analysis.

Primer design and PCR

The nucleotide sequence for CTSC gene was retrieved from NCBI (NG_007952.1), which is 51182 bp linear DNA. The primers were designed for all the 7 exons, which encode for Dipeptidyl – peptidase I. The primers were designing was done considering that no exonic region was left unread during automated sequencing.. Exon 1 to 6 were covered by a single set of primers whereas exon 7 was amplified with three overlapping primer sets (Table 1).

Table 1
PCR primers for all the exons of CTSC Gene.

Exon Number	Exon Length	Primer Name	Primer Sequence	Binding site (contig NG_007952.1)	Annealing Temperature (°C)	Amplicon Size
1	273	PLS 1F	CCAAGTCCCCGTTTCAGAG	4909–4927	60.0	451
		PLS 1R	GGGGGAAGCGGTAGTTGG	5342–5359		
2	146	PLS 2F	CAGGAAGTGTGTTGAGGCAAC	7517–7536	59.4	452
		PLS 2R	TCTTGGAAGAGTGGTGTCA	7949–7968		
3	167	PLS 3F	CAGTGTAACCTCTCAGGGTGAA	30090–30111	59.4	456
		PLS 3R	TGGTCAATTTATTTTCCAGTAAGG	30526–30545		
4	156	PLS 4F	ACATGCCAGGCTGTTCTAGG	33297–33316	60.4	450
		PLS 4R	CGTTAACAGATCACATAAAAAGTTACA	33729–33746		
5	116	PLS 5F	GTAATTGACACATTGAATCACTCATAA	41969–41995	60.4	430
		PLS 5R	GGAAAGAATAATTCATAGGCCACCT	42374–42398		
6	132	PLS 6F	TATTCCTCCATCACCCAACC	46221–46240	60.0	444
		PLS 6R	GATGCAGTAGAGAGAGCGCA	46791–46810		
7	917	PLS 7.1F	GGAAAATGGATGGATGAATGA	48116–48136	57.0	450
		PLS 7.1R	AAGGGTCTCTTAGACCAAGTGTGG	48543–48565		
		PLS 7.2F	CCCATGGCAGTTGCTTTT	48481–48498	56.7	435
		PLS 7.2R	AGGGCAGTTTTAATTCTGAAGACA	48892–48915		
		PLS 7.3F	TCAGTTGTAAAGGGGAATTGG	48802–48822	55.8	486
		PLS 7.3R	TCTTCAAATGCTTTTCCTTCTT	49266–49287		

PCR was carried out in 20 µl reaction mixture consisting of 0.4 µl of 10 mM dNTP mix, 1 µl of 1 mM MgCl₂, 0.5 µl Primers- forward and reverse each of 5 pmol, 1 µl template of 100 ng, 5X Taq Buffer 4 µl, Taq enzyme 0.2 µl (BioRad)

iProof High Fidelity Cat No.172–5302) the final volume was adjusted to 20 µl with molecular biology grade water (G-Biosciences Cat. No. 786-72C). The amplification conditions were as follows: 30 seconds at 98 °C for one cycle, followed by 35 cycles of 10 seconds at 98 °C, 30 sec at annealing temperature (Table 1) for respective primers and 15 seconds at 72 °C. Final extension was carried out at 72 °C for 5 minutes (Eppendorf Mastercycler Gradient- Germany).

Sequencing of the PCR amplicons

The amplified PCR products were subjected to automated sequencing ABI-3130E at Center for Cellular and Molecular Biology, Hyderabad, India. All the amplicons including the affected and normal were sequenced. However, we could not rule out a mutation in the intronic sequence that would lead to abnormal splicing of the transcript, or a mutation in nearby regulatory sequences that could reduce gene expression.

Results

All the patients (PLS1, PLS2, PLS3, PLS7, PLS8, PLS12, PLS13) having severe palmar plantar keratoderma and periodontitis, and their unaffected family members (PLS4, PLS5, PLS6, PLS9, PLS10, PLS11, PLS14) were analysed for mutations in the CTSC gene in all the 7 exons. The mutations were observed in only in exon 2,3,5,6. Exon 1, 4, 7 don not show any mutation. Table 2 represents mutation spectrum in exon 2. It is clear that all the 14 samples show missense mutation in the same nucleotide base position namely, 7613A > T and 7890C > A. The mutations 7613A > T results in amino acid change K2538I, whereas mutation 7890A > T results in amino acid change N2630K. The mutation spectrum in exon 3 is depicted in Table 3. It is clear from the table that all the 14 individuals show a frame shift mutation in base change 30126–30127 ins A with no amino acid change. Table 4 shows mutation spectrum in exon 5. All the 14 individuals show a missense mutation with the base change 42281T > C resulting in amino acid change L14094S. The mutation spectrum in exon 6 is represented in Table 5. It is clear that only 5 individuals out of 14 show missense mutation. The base change 46325A > G resulting in amino acid change E154424 was observed in PLS 1, PLS4, PLS5, PLS6, PLS7. And base 46375A > G with amino acid change M15453 was found in PLS – 1, 4, 5, 6, 7. Whereas base change 46663C > T with no amino acid change was found in PLS- 4, 5 and base change 46519G > T resulting in amino acid change A15307S was found in PLS 5, 6, 7.

Table 2
Mutation analysis of exon 2.

Specimen	Base change	Position	Length	Type	Effect	Aa change
PLS-1	7613A > T	7613	1	Sub	Missense	K2538I
PLS-2	7613A > T	7613	1	Sub	Missense	K2538I
PLS-3	7613A > T	7613	1	Sub	Missense	K2538I
PLS-4	7613A > T	7613	1	Sub	Missense	K2538I
PLS-5	7613A > T	7613	1	Sub	Missense	K2538I
PLS-6	7613A > T	7613	1	Sub	Missense	K2538I
PLS-7	7613A > T	7613	1	Sub	Missense	K2538I
PLS-8	7613A > T	7613	1	Sub	Missense	K2538I
PLS-9	7613A > T	7613	1	Sub	Missense	K2538I
PLS-10	7613A > T	7613	1	Sub	Missense	K2538I
PLS-11	7613A > T	7613	1	Sub	Missense	K2538I
PLS-12	7613A > T	7613	1	Sub	Missense	K2538I
PLS-13	7613A > T	7613	1	Sub	Missense	K2538I
PLS-14	7613A > T	7613	1	Sub	Missense	K2538I
PLS-1	7890C > A	7890	1	Sub	Missense	N2630K
PLS-2	7890C > A	7890	1	Sub	Missense	N2630K
PLS-3	7890C > A	7890	1	Sub	Missense	N2630K
PLS-4	7890C > A	7890	1	Sub	Missense	N2630K
PLS-5	7890C > A	7890	1	Sub	Missense	N2630K
PLS-6	7890C > A	7890	1	Sub	Missense	N2630K
PLS-7	7890C > A	7890	1	Sub	Missense	N2630K
PLS-8	7890C > A	7890	1	Sub	Missense	N2630K
PLS-9	7890C > A	7890	1	Sub	Missense	N2630K
PLS-10	7890C > A	7890	1	Sub	Missense	N2630K
PLS-11	7890C > A	7890	1	Sub	Missense	N2630K
PLS-12	7890C > A	7890	1	Sub	Missense	N2630K
PLS-13	7890C > A	7890	1	Sub	Missense	N2630K
PLS-14	7890C > A	7890	1	Sub	Missense	N2630K

Table 3
Mutation analysis of exon 3.

Specimen	Base change	Position	Length	Type	Effect	Aachange
PLS-1	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-2	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-3	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-4	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-5	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-6	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-7	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-8	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-9	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-10	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-11	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-12	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-13	30126-30127insA	30126	1	Ins	Frameshift insertion	–
PLS-14	30126-30127insA	30126	1	Ins	Frameshift insertion	–

Table 4
Mutation analysis of exon 5.

Specimen	Base change	Position	Length	Type	Effect	Aa change
PLS-1	42281T > C	42281	1	Sub	Missense	L14094S
PLS-2	42281T > C	42281	1	Sub	Missense	L14094S
PLS-3	42281T > C	42281	1	Sub	Missense	L14094S
PLS-4	42281T > C	42281	1	Sub	Missense	L14094S
PLS-5	42281T > C	42281	1	Sub	Missense	L14094S
PLS-6	42281T > C	42281	1	Sub	Missense	L14094S
PLS-7	42281T > C	42281	1	Sub	Missense	L14094S
PLS-8	42281T > C	42281	1	Sub	Missense	L14094S
PLS-9	42281T > C	42281	1	Sub	Missense	L14094S
PLS-10	42281T > C	42281	1	Sub	Missense	L14094S
PLS-11	42281T > C	42281	1	Sub	Missense	L14094S
PLS-12	42281T > C	42281	1	Sub	Missense	L14094S
PLS-13	42281T > C	42281	1	Sub	Missense	L14094S
PLS-14	42281T > C	42281	1	Sub	Missense	L14094S

Table 5
Mutation analysis of exon 6.

Specimen	Base change	Position	Length	Type	Effect	Aa change
PLS-1	46325A > G	46325	1	sub	Missense	E15442G
PLS-1	46357A > G	46357	1	Sub	Missense	M15453V
PLS-4	46325A > G	46325	1	Sub	Missense	E15442G
PLS-4	46357A > G	46357	1	Sub	Missense	M15453V
PLS-4	46663C > T	46663	1	Sub	Missense	–
PLS-5	46325A > G	46325	1	Sub	Missense	E15442G
PLS-5	46357A > G	46357	1	Sub	Missense	M15453V
PLS-5	46519G > T	46519	1	Sub	Missense	A15507S
PLS-5	46663C > T	46663	1	Sub	Missense	–
PLS-6	46325A > G	46325	1	Sub	Missense	E15442G
PLS-6	46357A > G	46357	1	Sub	Missense	M15453V
PLS-6	46519G > T	46519	1	Sub	Missense	A15507S
PLS-7	46325A > G	46325	1	Sub	Missense	E15442G
PLS-7	46357A > G	46357	1	Sub	Missense	M15453V
PLS-7	46519G > T	46519	1	Sub	Missense	A15507S

Discussion

The results of the present study clearly indicate that, among the seven PLS patients studied, mutations in the CTSC gene are observed only in exons 2, 3, 5 and 6. The exons 1, 4 and 7 do not show any mutations in this population.

The mutation spectrum shows that, in exon 2, 5 and 6 only missense mutations and in exon 3 only frame shift insertion are observed. Hence the total numbers of mutations observed in this study are 6. Out of these 5 are missense mutations and 1 is a frame shift insertion.

All the six nucleotide changes reported in this study fulfilled the criteria of a mutation, as these changes were not present in the reference-sequence of the CTSC which encodes for the enzyme dipeptidyl-pentidase 1 (NG_007952.1). In this study total 14 individuals were analyzed for mutations in CTSC gene. Out of 14 the individuals PLS1, PLS2, PLS3, PLS7, PLS8, PLS12 and PLS 13 were exhibiting extreme phenotype of PLS. Rest of the subjects were from the same family but not having any clinical features of PLS. PLS1 – PLS5 belong to family 1, PLS6- PLS8 belong to family 2 and PLS 10–14 belong to family 3.

The missense mutation g.7613A > T was found in exon 2 of PLS 1 which results in amino acid change K2538I. The same mutation was also found in PLS2, PLS10, PLS11, PLS12, PLS13 and PLS14. Further this mutation was found in 4 PLS affected individuals and in 3 non-PLS family members. This may suggest that g.7613A > T may be a recessive mutation causing pathogenicity only in homozygous condition. Moreover, the mutation g.7613A > T is never reported earlier and hence this is a novel mutation reported from South Indian families. The amino acid change K2538I is expected to cause structural alterations of the CTSC protein which may ultimately pave way for the development of PLS.

Similarly mutation g.7890C > A was found in PLS affected individuals PLS1, PLS2, PLS12, PLS13 and also in non-PLS individuals PLS10, PLS11, and PLS14. This mutation is also present in all the family members of the PLS family 1 and 3. This may suggest that a complex interaction of genetics and environment may result in manifestation of clinical features of PLS. Apart from the aforementioned mutations a frame shift mutation g.7580delA was found in PLS10 which is non-PLS subject. Both mutation g.7890C > A and g.7580delA have never been reported and are novel identifications of this study.

PCR products of Exon 3 were analyzed for all the 14 individuals of PLS families g.30126–30127 insA was found in all the affected as well as non-affected members of the PLS families. The insertion was found to cause the frame shift insertion and not leading to any amino acid change as reading frame change. The said frame shift insertion is also never been reported in past published studies. However, this insertion was not found in any family members of PLS 2 family.

The mutation g.42281T > C was found in exon 5 in all the 14 members of the all the PLS families. This is a missense mutation leading to the amino acid change L14094S. This is the novel mutation found in our study in all the family members and never been reported elsewhere. Comparing with the reference sequence it was found that the mutation g.42281T > C is restrict to the Indian PLS family members. The change in amino acid is expected to change the structure of the protein dipeptidyl-pemtpidase1. But when the mutation is present in all the affected and non affected PLS individuals it is also suspected that only these mutations are not responsible for causing the phenotypic changes but also some other mutations or expressions of genes are responsible for causing PLS.

In exon 6 of PLS1, mutation g.46325A > G and G46357A > G were found. Both the mutations are missense mutation and leading to the amino acid change E15442G and M15453V respectively. The mutation g.4625A > G is novel mutation found in exon 6 of specimen 1, whereas the mutation g.46357A > G has been already reported in Indian families [13] and in Spanish families[14].

The mutation g.46325A > G, g.46357A > G and g.46663C > T were found in specimen 4. Among the 3 mutations in specimen 4. The mutations g.46357A > G and g.46663C > T were already reported in the earlier studies [13] in Indian families as well as in Turkish families.

In exon 6 of specimen 5, mutation g.46325A > G, g.46357A > G, g.46519G > T and g.46663C > T has been reported. All the 4 mutation were missense mutations and leading to the amino acid change. The mutations g.46357A > G and g.46663C > T were already reported and rest of the two mutations are novel found in our study.

In exon 6 of specimen 6, mutations g.46325A > G, g.46357A > G and g.46519G > T were reported. Among the 3 mutations, mutation g.46357A > G has been already reported and the rest of the two mutations are novel. All the mutations are missense and leading to the aminoacid change E15442G, M15453V and A15507S respectively.

In exon 6 of specimen 7, mutations g.46325A > G, g.46357A > G and g.46519G > T were observed. The mutation g.46325A > G and g.46357A > G were found in the specimen PLS1, PLS4, PLS5, PLS6 and PLS7

An interesting feature of the CTSC gene is that mutations in this gene also result in two other closely related conditions: the Haim-Munk Syndrome [15], and prepubertal periodontitis[15]. A common clinical manifestation in all three syndromes is severe early-onset periodontitis. Haim-Munk syndrome (HMS) is an ethnically specific disorder described only in Jews of South Indian origin (the so called "Cochin Jews"). The clinical phenotypes of HMS overlap with PLS and prepubertal periodontitis (PPP) and include congenital keratosis palmoplantaris, onychogryposis, periodontitis, pes planus, arachnodactyly, and acroosteolysis. Thus HMS, PPP and PLS seem to be allelic variants. A common mutation c.1040A > G has been shown to cause two distinct phenotypes, PLS and PPP, suggesting that other factors such as

genetic or environmental, play a role in the ultimate phenotype. A missense mutation c.857A > G (p.Q286R) in the CTSC gene has been found to cause HMS [15]. This mutation has also been detected in a homozygous state in a Spanish PLS patient, suggesting that the HMS and PLS are clinical variants of the same homozygous cathepsin C gene mutation [14]. It is possible that a part of the clinical manifestations in HMS patients (viz., hyperkeratosis and periodontitis) is caused by a mutation in the CTSC gene where as other features of HMS (viz., onychogryposis, pes planus, arachnodactyly, and acroosteolysis) are caused by mutations in another hitherto undescribed gene. However, this possibility remains to be proven. Hart et al. have carried out genotype-phenotype correlation using 22 probands on whom genotype and phenotype data were available. The categories for genotype were mutations in the pro-region and mutations in the mature enzyme. The categories for phenotypes were the presence or absence of transgressions of the hyperkeratosis lesions on the knees and elbows [14]. No correlation was found as affected subjects with transgressions of dermal lesions onto knees or elbows or both had mutations in both the pro- and mature regions of the enzyme. Our analysis also did not find any correlation between the types of mutations (missense, nonsense, insertion, deletion and splice site) and the presence or absence of the lesions on the knees or elbows or both as observed previously [14].

Conclusion

Even though we have identified many mutations in different exonic regions of the CTSC gene, it is not possible to develop any biomarker for early detection as carrier deletion of PLS because mutations were randomly present in all the PLS affected and non-affected individuals. To develop specific biomarkers more number of samples have to be studied and it is practically not possible as the frequency of the PLS is 4 in million. Moreover mutations in the promoter region and intronic region may also contribute to the development of PLS. Apart from mutations which are caused by change in nucleic acid sequences, epigenetic modifications can also be an important etiological factor. Advanced technologies like whole genome sequencing and genome wide association studies may lead the way in exploring the proper root cause.

The results of this study with all its lacunas reaffirm the role of CTSC gene in manifestation of PLS. But the exact mechanism and the dynamics of disease prognosis can be understood only by conducting a multifaceted research encompassing a larger pool of subjects spread across a bigger geographical area.

Abbreviations

LIST OF ABBREVIATIONS:

PLS- Papillion Lefevre Syndrome.

CTSC- cathepsin C.

EST-Expressed Sequence Tag.

DNA- Deoxyribonucleic acid.

PCR- polymerase chain reaction.

EDTA- Ethylenediaminetetraacetic acid.

NCBI- National Center for Biotechnology Information.

dNTPs- Deoxynucleoside triphosphates.

MgCl₂ - Magnesium chloride.

μl- Micro liter.

mM- micro Molar.

Declarations

Ethical approval- Ethical approval for the study was obtained from Institutional Ethical Committee (IEC) of Karnataka Institute for DNA Research (KIDNAR), Dharwad. Karnataka, India.

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Consent for Publication- Detailed informed consent was obtained from each participant before sample and data collection in our institutional consent form.

Availability of Data and Material- Not applicable.

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Authors Contribution-

SK and PPG contributed for sample collection and laboratory work. GA helped in clinical diagnosis. PG designed the work and verified the data analysis.

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Figures

Figure 1

PLS1 showing Periodontitis affecting secondary dentition.

Figure 2

PLS3 radiograph showing Orthopantomogram of oral cavity with severe periodontitis

Figure 3

PLS7 showing Periodontitis.

Figure 4

PLS8 showing Knee hyperkeratosis in the patient.

Figure 5

PLS12 showing Plantar hyperkeratosis.

Figure 6

PLS13 showing Palmar hyperkeratosis.