

## Papillon-Lefevre Syndrome (PLS) via CTSC gene sequencing Test #772

**Brief Description of Clinical Features:** Papillon-Lefevre Syndrome (PLS, OMIM 245000) is characterized by palmoplantar hyperkeratosis (thickening of skin on palms and soles of feet) and severe early onset periodontitis resulting in the premature loss of primary and secondary teeth (Gorlin et al. *J Pediatr* 65:895-908, 1964; Haneke *Hum Genet* 51:1-35, 1979). Palmoplantar keratosis usually develops in PLS patients by 3 years of age and varies from mild scaly skin to overt hyperkeratosis. Clinically, it is the periodontitis that distinguishes PLS from other forms of palmoplantar keratosis. The periodontitis of PLS is generally very aggressive and unresponsive to therapies, though in some very rare cases periodontitis is mild or late onset (Fardal et al. *J Clin Periodontol* 25:181-184, 1998). Consequently, most PLS patients lose all of their teeth by 20 years of age. PLS is ascertained mainly by dentists because of the severe periodontitis. Teeth are affected in the order of eruption and accompanied by inflamed periodontal tissue, bleeding of gums, pocket formation, and loosening with no sign of root resorption. In addition, some PLS patients may be more susceptible to infections because of an aberrant immune response (Haneke *Hum Genet* 51:1-35, 1979).

**Genetics:** PLS exhibits an autosomal recessive pattern of inheritance and is caused by mutations in the *CTSC* gene (Hart et al. *J Med Genet* 36:881-887, 1999; Toomes et al. *Nat Genet* 23:421-424, 1999). The frequency of PLS is approximately 1-4/ million people (Gorlin et al. *J Pediatr* 65:895-908, 1964). *CTSC* encodes cathepsin C (CTSC), a lysosomal protease and endopeptidase. *CTSC* is expressed in tissues involved in the immune response, e.g. bone marrow derived myeloid and lymphoid cells, and plays an essential role in protein degradation and pro-enzyme activation including activation of granule serine proteases involved in a variety of immune responses (McGuire *J Biol Chem* 268:2458-2467, 1993; Rao et al. *J Biol Chem* 272:10260-10265, 1997). Consequently, loss of functional *CTSC* may be linked to an attenuated host response against bacteria in dental plaque and susceptibility to periodontitis (see Toomes et al. *Nat Genet* 23:421-424, 1999, for discussion). Causative mutations in the *CTSC* gene include numerous missense and nonsense mutations, and to a lesser extent splicing mutations, insertions, and deletions. No predominant mutations have been reported, and there is no obvious genotype-phenotype correlation.

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of the 7 coding exons of the *CTSC* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence any single exon (Test #100) or two exons (Test #200) in family members of patients with known mutations, or to confirm research results (\$190-340).

**Reference Sequences:** Genomic: NC\_000011.9 mRNA: NM\_001814.4 Protein: NP\_001805.3 (CCDS 8282.1)

**Indications for Test:** Individuals with periodontitis, palmoplantar keratosis, and anyone with a family history of PLS or severe and rapid tooth loss.

**Sensitivity of Test:** No mutations in genes other than *CTSC* have been reported to cause PLS.

**Turnaround Time:** Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

**Specimen Requirements:** See page 4 of Requisition Form

**Price: Sequencing of CTSC \$ 570**

CPT Codes							
Test	83890 x1	83891 x1	83898 x8	83904 x8	83894 x1	83912 x1	Total
<i>CTSC</i>	\$30	\$40	\$150	\$230	\$30	\$90	\$570

**Accreditation:** CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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