CTSC Gene Analysis in Papillon- Lefèvre Syndrome (PLS) and Haim-Munk Syndrome (HMS)

Clinical Features:
Papillon-Lefèvre Syndrome (PLS) is characterized by two main features: palmoplantar keratoderma (PPK) with thickening (hyperkeratosis) of the skin of palms and soles, and severe, early-onset periodontitis leading to the premature loss of dentition. The destruction of the periodontium results in loss of primary teeth usually by age 5 and loss of permanent teeth by about age 20. The PPK can range from mild or psoriasiform scaling to severe hyperkeratosis, which usually develops before age 3. Hyperkeratotic plaques may also develop over elbows and knees. Other symptoms of PLS may include pyogenic skin infections, nail dystrophy, hyperhidrosis, increased susceptibility to infection, and ectopic cranial calcifications.

Haim-Munk Syndrome (HMS) is also associated with PPK similar to PLS, but features additional abnormalities, including arachnodactyly, acro-osteolysis, nail deformities (onychogryphosis), and more severe skin involvement. HMS has only been seen in descendants of an isolated non-Ashkenazi Jewish isolate from Cochin, India. PLS and HMS are both syndromic forms of PPK, and can be distinguished from other types of PPK by the characteristic severe, early-onset periodontitis.

Inheritance Pattern/Genetics:
Autosomal recessive

Pathogenic variants in the CTSC gene cause Papillon- Lefèvre Syndrome and Haim-Munk Syndrome. The gene is located on chromosome 11q14.2 and contains seven exons. CTSC encodes cathepsin C, a lysosomal cysteine protease with four identical subunits that are important for intracellular protein degradation and activation of serine proteases in immune inflammatory cells. CTSC is highly expressed in lung, kidney, placenta, myeloid, and immune cells.

Test Methods:
Using genomic DNA from a submitted specimen, bi-directional sequence analysis of the complete coding region (exons 1-7) and splice sites of the CTSC gene is performed. If no variant is found by sequencing, targeted array CGH analysis is available to evaluate for a deletion or duplication of one or more exons in the CTSC gene. The presence of a variant or deletion is confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.
Test Sensitivity:
One study identified pathogenic CTSC variants in 30 out of 36 families with PLS, indicating a clinical sensitivity of ~83%. In the majority of reported patients with PLS and HMS, pathogenic variants in both CTSC alleles were identified by gene sequencing. However, one study did identify a large deletion, which would not be identifiable by sequencing.

References: