**GJB2 (Connexin-26) gene analysis for autosomal dominant palmoplantar keratoderma associated with hearing loss and non-syndromic autosomal dominant or recessive hearing loss**

**Related Disorders:** Missense variants in Connexin 26 (Cx26; GJB2) are associated with different forms of palmoplantar keratoderma (PPK) with hearing loss, including Vohwinkel syndrome, Bart-Pumphrey syndrome, and Keratitis-Ichthyosis-Deafness (KID) syndrome. In addition, pathogenic variants in GJB2 may also cause autosomal dominant or recessive non-syndromic hearing loss.

**Clinical Features:**
Both the skin findings and the hearing loss have a heterogeneous clinical presentation in these disorders. In some cases the deafness is congenital. In others there is later onset hearing loss of moderate degree\(^1\). The skin features associated with hearing loss and GJB2 variants are also variable: in Vohwinkel syndrome there is diffuse honeycomb hyperkeratosis of palms and soles with typical starfish keratoses on the dorsum\(^1,2\). Pseudo-ainhum (constricting bands) and auto-amputation of digits may occur\(^1\). The skin features of Bart-Pumphrey syndrome include hyperkeratotic plaques over knuckles and the dorsal digital joints (knuckle pads), leukonychia (white nails) and palmoplantar keratoderma\(^3\). Keratitis-Ichthyosis-Deafness syndrome is an ectodermal dysplasia affecting the skin, hearing and vision and testing information is provided separately\(^2,3\).

Pathogenic variants in the GJB2 gene account for up to 50% of all autosomal recessive nonsyndromic sensorineural hearing loss\(^4,5\). The hearing loss in these patients has been described as prelingual, symmetric, non-progressive, and with varied severity ranging from mild to profound hearing loss\(^6-8\). While studies have shown that approximately 10-50% of patients with GJB2 variants are heterozygous for a single variant\(^4\), 7-16% of these individuals were also found to be heterozygous for a 342 kb deletion including the GJB6 gene\(^4,5\). Therefore, if a single variant is the only finding by GJB2 sequence analysis, deletion/duplication analysis including the GJB6 gene is indicated.

**Genetics:**
Sequence variants in GJB2 can lead to autosomal dominant or recessive hearing loss, either non-syndromic or associated with skin and nail findings. This test is designed to detect sequence variants associated with skin findings and hearing loss.
Test Information Sheet

Test Methods:
Using genomic DNA, the coding sequence and splice junctions of GJB2 gene are amplified by polymerase chain reaction and then sequenced bi-directionally using capillary sequencing. If a sequence change is identified, the variant is confirmed in a separate reaction by capillary sequencing.

Test Sensitivity:
If there is a variant in the coding sequence of GJB2 in an individual, the methods employed by GeneDx will identify the variant approximately 99% of the time. However, the test being performed will not identify variants that exist in a region of the gene not covered by this test or in any other gene. In case no variant has been identified in GJB2, GeneDx also offers testing of the Cx30 gene, GJB6.

References: