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 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:

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