

## *GJB6* (Connexin-30) Gene Analysis in Clouston syndrome and Other *GJB6*-Related Disorders

**Disorder also known as:** Hidrotic ectodermal dysplasia; Autosomal dominant deafness (DFNA3B); Autosomal recessive deafness 1B (DFN1B); May also be involved in digenic deafness

### **Clinical Features:**

In contrast to the much more common X-linked form of ectodermal dysplasia, most of patients with a *GJB6*-related autosomal dominant form of hidrotic ectodermal dysplasia have normal sweat and sebaceous gland function. Frequent clinical manifestations include partial to total alopecia, nail hypoplasia and nail deformities, skin hyperpigmentation particularly over the joints, and palmoplantar keratoderma <sup>1-4</sup>.

Although not common, *GJB6* missense changes have been reported in individuals with autosomal dominant sensorineural hearing loss (DFNA3) <sup>5,6</sup>. Sequence variants in the *GJB6* gene account for approximately 10% of the variants associated with DFNA3 <sup>7</sup>. Hearing loss in DFNA3 is described as progressive, prelingual, and moderate to severe, while *GJB2*-related, nonsyndromic, autosomal recessive hearing loss (DFNB1) is described as prelingual, symmetric, non-progressive, ranging from mild to profound severity <sup>8-10</sup>. In patients with DFNB1, in whom only one *GJB2* variant was identified by sequencing, 7-16% were heterozygous for a common 342 kb deletion including the *GJB6* gene <sup>11,12</sup>.

### **Genetics:**

The *GJB6* gene encodes the Gap Junction protein Beta-6 (Connexin 30) protein. Pathogenic variants in this gene are associated with autosomal dominant disorders, although autosomal recessive inheritance has been described.

There are two very common variants in the *GJB6* gene, G11R and A88V. G11R is the cause of Hidrotic Ectodermal Dysplasia in all French-Canadians families tested to date, and also in many families originating from other geographical areas of the world. The A88V variant has been described in patients from India, Malaysia and Wales. Variants G11R and A88V have also been found in patients with thickened, pachyonychia congenital-like nails. A third variant, V37E, has been associated with disorders with overlapping features, Clouston syndrome and Keratitis-Ichthyosis-Deafness syndrome (KIDS) and congenital atrichia. Some families with high-frequency hearing loss but without other features of hidrotic ectodermal dysplasia have been found to have other variants in the *GJB6* gene.

## Test Methods:

Using genomic DNA, the coding sequence and splice junctions of *GJB6* 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 sequence variant in the coding sequence of *GJB6* 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, in any other gene, or large genomic deletions involving *GJB6*, which have been associated with autosomal recessive sensorineural hearing loss. However, deletion/duplication analysis of the *GJB6* gene is available as a separate test.

In case no variant has been identified in *GJB6*, GeneDx also offers testing of the *Cx26* gene,

## References:

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