

## Variant: *NM\_004004.5(GJB2):c.235delC (p.Leu79Cysfs)*

Version: 1.0

[CA127025](#)

[17014 \(ClinVar\)](#)

**Gene:** GJB2 ([HGNC:2706](#))

**Condition:** nonsyndromic genetic deafness ([MONDO:0019497](#))

**Inheritance Mode:** Autosomal recessive inheritance

**UID:** eda5030c-9ccf-4b14-bada-077b25b2562c

**Approved on:** 2018-09-14

**Published on:** 2019-07-17

### *HGVS expressions*

**NM\_004004.5:c.235delC**

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NM\_004004.5(GJB2):c.235delC (p.Leu79Cysfs)

NC\_000013.11:g.20189349del

CM000675.2:g.20189349del

NC\_000013.10:g.20763488del

CM000675.1:g.20763488del

NC\_000013.9:g.19661488del

NG\_008358.1:g.8629del

ENST00000382844.2:c.235del

ENST00000382848.5:c.235del

ENST00000382844.1:c.235del

ENST00000382848.4:c.235del

NM\_004004.6:c.235del

**Pathogenic**

Met criteria codes **4**

**PM3\_Very Strong** **PS3\_Moderate**

**PVS1** **BS1**

Not Met criteria codes **3**

**BA1** **PP3** **PM2**

Evidence Links **3**

Expert Panel

[Hearing Loss VCEP](#)

Criteria Specification Information **!**

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

### *Hearing Loss VCEP*

The filtering allele frequency of the p.Leu79CysfsX3 variant in the GJB2 gene is 0.55% (121/ 18870) of East Asian chromosomes by the Genome Aggregation Database (<http://gnomad.broadinstitute.org>; calculated by using inverse allele frequency at <https://www.cardiodb.org/allelefrequencyapp/>), which is a high enough frequency to be classified as benign based on thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss variants (BS1). The ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for nonsyndromic hearing loss outweighs the high allele frequency of the variant in population databases. Therefore, the BS1 code will not contribute to the overall classification. The p.Leu79CysfsX3 variant in GJB2 is

predicted to cause a premature stop codon in the only exon of the gene, leading to absent protein in a gene in which loss-of-function is an established mechanism (PVS1). This variant has been detected in patients with hearing loss in trans with at least 4 pathogenic or suspected-pathogenic variants (PM3\_VS; PMID: 10983956, 10633133). A dye transfer assay, a functional study, has shown that the variant impacts protein function (PS3\_M; PMID: 12352684). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive nonsyndromic hearing loss based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PVS1, PM3\_VS, PS3\_M, BS1.

#### Met criteria codes

##### PM3\_Very Strong



This variant was identified in >10 individuals with a pathogenic variant in trans. See the individuals publication notes below for case counts.

147 Korean patients with NSHL were screened for variants in GJB2. The c.235delC variant was identified in 5 homozygous individuals and 5 compound hets. Because the het individuals did not have a second variant listed, I would only count the homozygous individuals here. [PubMed:10983956](#)

This is a mutation analysis for Japanese non-syndromic hearing loss. The c.235delC variant was identified in 7 affected families. Two families were homozygous, three families were compound het for Y136X, and two families were compound het for R143W. [PubMed:10633133](#)

##### PS3\_Moderate



A dye transfer assay demonstrated that there was no dye transfer in cells transfected with the c.235delC variant.

HeLa cells were transfected with WT, mock transfected cells, or c.235delC constructs. Lucifer yellow was incubated with the cells for the dye transfer assay. Cells with the WT GJB2 demonstrated dye transfer, the negative control and the c.235delC cells had no dye transfer. [PubMed:12352684](#)

##### PVS1



There are no alternate transcripts, the variant should results in NMD and lack of protein.

##### BS1



Although the MAF (using the ExAC FAF) is .38% in East Asians, BS1 is not contributing to the overall pathogenicity because this variant is on the HL ClinGen CDWG exclusion list.

#### Not Met criteria codes

##### BA1



Although the MAF (using the ExAC FAF) is .38% in East Asians, BS1 is not contributing to the overall pathogenicity because this variant is on the HL ClinGen CDWG exclusion list.

##### PP3



No splicing change predicted by MaxEntScan.

##### PM2



Although the MAF (using the ExAC FAF) is .38% in East Asians, BS1 is not contributing to the overall pathogenicity because this variant is on the HL ClinGen CDWG exclusion list.

[Curation History](#)

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