The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_004004.5(GJB2):c.235delC (p.Leu79Cysfs)

CA127025

17014 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: eda5030c-9ccf-4b14-bada-077b25b2562c
Approved on: 2018-09-14
Published on: 2018-12-10

HGVS expressions

NM_004004.5(GJB2):c.235delC (p.Leu79Cysfs)
NM_004004.5:c.235del
NM_004004.5:c.235delC
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
NM_004004.6:c.235del
ENST00000382844.1:c.235del
ENST00000382848.4:c.235del

Pathogenic

The Expert Panel has overridden the computationally generated classification - "*Uncertain Significance - Conflicting Evidence*"

Met criteria codes 4

PVS1 PS3_Moderate BS1 PM3_Very Strong

Not Met criteria codes 3

PP3 BA1 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

PVS1	✔	There are no alternate transcripts, the variant should results in NMD and lack of protein.
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
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.
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. 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 147 Korean patients with NSHL were screened for variants in GJB2. The c.235delC variant was identifed 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

Not Met criteria codes

PP3	✖	No splicing change predicted by MaxEntScan.
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.
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

Showing 1 to 1 of 1 rows

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