

Variant: *NM_004004.6(GJB2):c.139G>A (p.Glu47Lys)*

Version: 2.0

CA387461835 [↗](#)

1806861 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 244b0757-c15a-42d5-bba0-fe65208c5339

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HGVS expressions

NM_004004.6(GJB2):c.139G>A (p.Glu47Lys)

NM_004004.6:c.139G>A

NC_000013.11:g.20189443C>T

CM000675.2:g.20189443C>T

NC_000013.10:g.20763582C>T

CM000675.1:g.20763582C>T

NC_000013.9:g.19661582C>T

NG_008358.1:g.8533G>A

ENST00000382844.2:c.139G>A

ENST00000382848.5:c.139G>A

ENST00000382844.1:c.139G>A

ENST00000382848.4:c.139G>A

NM_004004.5:c.139G>A

Pathogenic

Met criteria codes 4

PM2_Supporting

PS3_Moderate

PM3_Very Strong

PP3

Not Met criteria codes 16

BS1

BS4

BS2

BP5

BP7

BP4

BP3

PVS1

PS1

PS4

BA1

PP1

PP4

PM1

PM5

PM4

Evidence Links 0

Expert Panel

Hearing Loss VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Hearing Loss Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CDH23, COCH, GJB2, KCNQ4, MYO6, MYO7A, SLC26A4,TECTA and USH2A Version 2.0

[↗](#) **PDF**

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Hearing Loss VCEP

The c.139G>A variant in GJB2 is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 47 (p.Glu47Lys). The highest population minor allele frequency in gnomAD v4.1.1 is 0.00008485% (1/1178590 -European [non-Finnish], PM2_Supporting met). The computational predictor REVEL yields a score of 0.971 (PP3 met). This variant has been detected in at least four

individuals with HL, who were compound heterozygous for the variant and pathogenic/likely pathogenic variants del(GJB6-D13S1830), c.299_300delAT (p.His100Argfs), c.235delC (p.Leu79fs), c.269T>C (p.Leu90Pro), confirmed in trans totaling 4.0 points (PM3_VeryStrong; PMIDs: 17666888, 19366456, 20234132, 21366436). Fluorescent dye assay studies in GJB2-expressing HEK293 and HeLa cells showed absent ionic and biochemical coupling (PS3_Moderate; PMIDs: 17146396, 26749107). In summary, based on the current evidence (PM3_VeryStrong, PS3_Moderate, PP3 & PM2_Supporting) this variant meets criteria to be classified as pathogenic for autosomal recessive nonsyndromic HL based on the ACMG/AMP criteria applied, as specified by the ClinGen HL-VCEP. (ClinGen Hearing Loss VCEP specifications version 2; 09/16/2026).

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.1 is 0.00008485% (1/1178590 -European [non-Finnish])
PS3_Moderate			Two independent fluorescent dye assay studies show absent ionic and biochemical coupling (PMIDs: 17146396, 26749107).
PM3_Very Strong			The variant was observed in trans with known pathogenic/likely pathogenic variants in at least four independent affected individuals across published literature (PMIDs: 17666888, 19366456, 20234132, 21366436).
PP3			The REVEL yields a score of 0.971.

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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