Variant: NM_004004.6(GJB2):c.109G>A (p.Val37Ile)

Version: 1.1

CA172210

17023 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 69193dd4-e172-4874-984a-28596f644cae
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HGVS expressions

NM_004004.6:c.109G>A
NM_004004.6(GJB2):c.109G>A (p.Val37Ile)
NC_000013.11:g.20189473C>T
CM000675.2:g.20189473C>T
NC_000013.10:g.20763612C>T
CM000675.1:g.20763612C>T
NC_000013.9:g.19661612C>T
NG_008358.1:g.8503G>A
ENST00000382844.2:c.109G>A
ENST00000382848.5:c.109G>A
ENST00000382844.1:c.109G>A
ENST00000382848.4:c.109G>A
NM_004004.5:c.109G>A

Pathogenic

Met criteria codes 3

PP1_Strong PS4 PM3

Not Met criteria codes 5

BS4 BS2 BA1 PS3 PP3

Evidence Links 1

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*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The filtering allele frequency (the lower threshold of the 95% CI of 143/1558, including 8 homozygous observations) of the c.109G>A (p.Val37Ile) variant in the GJB2 gene is 7.9% for East Asian genomes in gnomAD.This is a high enough frequency that, in the absence of conflicting data, might warrant a benign classification based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for

autosomal recessive hearing loss variants (BA1). However, based on the evidence outlined below, the ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for nonsyndromic hearing loss outweighs its high allele frequency in population databases. Therefore, the BA1 code will not contribute to the overall classification. The homozygous genotype and compound heterozygous genotype with another variant in GJB2 have shown to be statistically enriched in patients with nonsyndromic sensorineural hearing loss compared to individuals representative of the general population in gnomAD and/or those who underwent carrier screening at Counsyl. (PS4; PMID: 31160754). This study also reported the variant in 139 homozygous affected probands, 17 affected probands with the p.Met34Thr variant in trans, 131 affected probands with a variant asserted to be P/LP in ClinVar, and 78 affected probands with a premature GJB2 termination codon in trans. However, because the variant is also very frequent in the general population, this criteria has been applied at the strength of Moderate. (PM3; PMID: 31160754). The p.Val37Ile variant in GJB2 has been reported to segregate with hearing loss in at least 21 family members (PP1_Strong; PMID: 31160754). Although homozygous or compound heterozygous observations have been identified in individuals with normal hearing, it has been suggested that individuals with the p.Val37Ile variant lose hearing at ~1dB/year, suggesting an age-related penetrance (PMID: 27308839). Furthermore, in dye transfer and electrical coupling assays, both functional studies have shown that the variant impacts protein function (PMID: 26088551, 12505163, 16300957) and knock-in mouse model demonstrated that the p.Val37Ile variant leads to the phenotype. However, because the codon for p.Val37 in mouse (GTG) was different from that in human (GTT), c.109G>A in mouse would translate into p.Val37Met, and the dye transfer and coupling assays have limited validation and correlation with pathogenicity, neither was not counted as functional evidence. (PMID: 27623246). Of note, the severity of hearing loss is known to be mild on average and there have been multiple accounts of incomplete penetrance of the variant in families/individuals with p.Val37Ile in a biallelic genotype. In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive nonsyndromic genetic hearing loss based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PS4, PP1_Strong, PM3.

Met criteria codes

PP1_Strong ✔

The collected literature review in Shen et al has found that the p.Val37Ile variant segregates with disease in at least 21 individuals.

The p.Val37Ile variant segregated with hearing loss in 21 individuals. PubMed:31160754

PS4 ✔

A case-control comparison was done by the HL group that demonstrated that this variant is highly enriched in cases v controls. For homozygotes the OR is 20 and the p value is <0.0001

This is the case-control paper from the HL VCEP that demonstrates significant enrichment of V37I in patients compared to controls. PubMed:31160754

PM3 ✔

Shen et al 2019 demonstrated in the combined analysis of at least 10 clinical sites that there were >120 compound heterozygotes with the p.Val37Ile variant. However, because the variant is also very frequent in the general population, the HL group decided to only apply this criteria at the usual strength of Moderate.

Not Met criteria codes

BS4 ✖

Although homozygous or compound heterozygous observations have been identified in hearing individuals, it has been suggested that individuals with the p.Val37Ile variant lose hearing at ~1dB/year, suggesting an age-related penetrance. Therefore, BS4 is not met.

The p.Val37Ile variant segregated with hearing loss in 21 individuals. PubMed:31160754

BS2 ✖

Although homozygous or compound heterozygous observations have been identified in hearing individuals, it has been suggested that individuals with the p.Val37Ile variant lose hearing at ~1dB/year (Wu 2017), suggesting an age-

related penetrance. Therefore, BS2 is not met.

BA1	ℹ	✖	Although the filtering allele frequency for the p.Val37Ile variant in East Asian alleles in gnomAD is 7.9% (1665/19952 with 96 homozygotes), the HL VCEP did not apply BA1 because of conflicting evidence, the ability for mild hearing loss to be underdiagnosed in population controls, and highly significant enrichment of the variant in cases with hearing loss compared to controls, meeting PS4.
PS3	ℹ	✖	Conduction experiments in Xenopus oocytes transfected with V37I demonstrate reduced conduction. There is a homozygous c.109G>A knock-in mouse model that demonstrates mild hearing loss that is more profound at high frequencies. However, the codon used in mice, when transferred to humans, is p.Val37Met, so it was not counted as strong functional evidence. Dye transfer was impaired in HEK293T cells transfected with the p.V37I variant.
PP3	ℹ	✖	Our REVEL cutoff is >0.7 and the score for p.V37I is 0.656

Curation History

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