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.71G>A (p.Trp24Ter)

CA172240

17002 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: b207d225-ce97-42b5-b04a-d9d420ada5eb
Approved on: 2018-09-17
Published on: 2018-12-10

HGVS expressions

NM_004004.5(GJB2):c.71G>A (p.Trp24Ter)
NM_004004.5:c.71G>A
NC_000013.11:g.20189511C>T
CM000675.2:g.20189511C>T
NC_000013.10:g.20763650C>T
CM000675.1:g.20763650C>T
NC_000013.9:g.19661650C>T
NG_008358.1:g.8465G>A
NM_004004.6:c.71G>A
ENST00000382844.1:c.71G>A
ENST00000382848.4:c.71G>A

Pathogenic

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

Met criteria codes 4

PVS1 BS1 PS3 PM3_Very Strong

Not Met criteria codes 19

BS4 BS2 BP7 BP5 BP2 BP4 BP3 PS1 PS4 PS2 BA1 PM5 PM4 PM1 PM2 PM6 PP3 PP1 PP4

Evidence Links 4

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.Trp24X variant in the GJB2 gene is 0.38% (137/ 30782) of South 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 likely benign based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss variants (BS1). However, 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.Trp24X variant in GJB2 is predicted to cause a premature stop codon in the only exon of GJB2 that leads to a truncated or 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: 15070423, 24123366, 18941476, 9139825). A knock-in mouse model demonstrates that the p.Trp24X variant leads to the phenotype (PS3; PMID:18941476). 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, BS1.

Met criteria codes

PVS1	✔	Nonsense change.
BS1	✔	Allele frequency 0.055% overall, 0.44% in South Asian - gnomAD On the exclusion list
PS3	✔	PMID 18941476 completed functional studies, and while this variant still allows for the creation of a protein, it gets stuck in cytoplasm and does not get trafficked to the membrane. completed functional studies, and while this variant still allows for the creation of a protein, it gets stuck in cytoplasm and does not get trafficked to the membrane. In addition, of the 520 individuals with non-syndromic, sensorineural hearing loss that they examined in this study, W24* was the most common mutation observed in this study, and accounted for 73% of all pathological mutations in the GJB2 gene. PubMed:18941476
PM3_Very Strong	✔	Many examples of the W24* variant found in trans with other nonsense or frameshifting GJB2 alleles. 530 individuals with nonzyndromic hearing loss from India sequenced. 74 individuals were homozygous for the W24* variant, 9 individuals were heterozygous for the variant, and 17 individuals were compound heterozygous for the variant. The second variant was not specified. PubMed:18941476 Family segregating with homozygous W24* variant in four individuals with hearing loss. PubMed:9139825 W24* was found in trans with GJB2 35delG variant in one deaf individual. Also found in trans in unaffected individuals with R127H variant. PubMed:15070423 Variant identified as homozygous in one individual with hearing loss. PubMed:24123366

Not Met criteria codes

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
BP7	✖	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
BP2	✖	530 individuals with nonzyndromic hearing loss from India sequenced. 74 individuals were homozygous for the W24* variant, 9 individuals were heterozygous for the variant, and 17 individuals were compound heterozygous for the

variant. The second variant was not specified. PubMed:18941476
Family segregating with homozygous W24* variant in four individuals with hearing loss. PubMed:9139825
W24* was found in trans with GJB2 35delG variant in one deaf individual. Also found in trans in unaffected individuals with R127H variant. PubMed:15070423
Variant identified as homozygous in one individual with hearing loss. PubMed:24123366

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
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
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	Allele frequency 0.055% overall, 0.44% in South Asian - gnomAD On the exclusion list
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
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✖	Allele frequency 0.055% overall, 0.44% in South Asian - gnomAD On the exclusion list
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	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

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.