Variant: NM_004004.5(GJB2):c.71G>A (p.Trp24Ter)

Version: 1.0

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
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HGVS expressions

NM_004004.5:c.71G>A
NM_004004.5(GJB2):c.71G>A (p.Trp24Ter)
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
ENST00000382844.2:c.71G>A
ENST00000382848.5:c.71G>A
ENST00000382844.1:c.71G>A
ENST00000382848.4:c.71G>A
NM_004004.6:c.71G>A

Pathogenic

Met criteria codes 4

PVS1 BS1 PM3_Very Strong PS3

Not Met criteria codes 22

PM6 PM2 PM1 PM5 PM4
BS4 BS3 BS2 BP5 BP7 BP4
BP3 BP1 BP2 PS1 PS2 PS4
BA1 PP1 PP2 PP3 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
PM3_Very Strong	✔	Many examples of the W24* variant found in trans with other nonsense or frameshifting GJB2 alleles. Family segregating with homozygous W24* variant in four individuals with hearing loss. PubMed:9139825 Variant identified as homozygous in one individual with hearing loss. PubMed:24123366 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 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
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

Not Met criteria codes

PM6	✖	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
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

BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	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.
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
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	Family segregating with homozygous W24* variant in four individuals with hearing loss. PubMed:9139825 Variant identified as homozygous in one individual with hearing loss. PubMed:24123366 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 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
PS1	✖	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
PS4	✖	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

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	✖	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
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