Variant: NM_004004.5(GJB2):c.35delG (p.Gly12Valfs)

Version: 1.0

CA127023

17004 (ClinVar)

Gene: GJB2 (HGNC:2706)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: 58892872-8c79-4342-854b-6878c83611db
Approved on: 2018-09-20
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HGVS expressions

NM_004004.5:c.35del
NM_004004.5:c.35delG
NM_004004.5(GJB2):c.35delG (p.Gly12Valfs)
NC_000013.11:g.20189552del
CM000675.2:g.20189552del
NC_000013.10:g.20763691del
CM000675.1:g.20763691del
NC_000013.9:g.19661691del
NG_008358.1:g.8429del
ENST00000382844.2:c.35del
ENST00000382848.5:c.35del
ENST00000382844.1:c.35del
ENST00000382848.4:c.35del
NM_004004.6:c.35del

Pathogenic

Met criteria codes 4

PS4 BA1 PVS1 PM3_Very Strong

Not Met criteria codes 22

PP1 PP2 PP3 PP4 PS1 PS2
PS3 PM1 PM5 PM4 PM6
PM2 BP5 BP7 BP4 BP3
BP1 BP2 BS1 BS4 BS3 BS2

Evidence Links 2

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.35delG variant in GJB2 is predicted to cause a premature stop codon in biologically-relevant-exon 2/2 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: 26445815). This variant was found to have a statistically higher prevalence in affected individuals over controls (PS4; PMID: 26969326, 25999548). The filtering allele frequency

of the c.35delG variant in the GJB2 gene is 0.9% for European (Non-Finnish) chromosomes in the Genome Aggregation Database (1207/124552 with 95% CI), 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 (BA1). The ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for hearing loss outweighs the high allele frequency of the variant in population databases. Therefore, the BA1 code will not contribute to the overall classification. In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive non-syndromic hearing loss based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PVS1, PM3_VS, PS4, BA1.

Met criteria codes

PS4	✓	In 1 large study (Sloan-Heggen 2015) and in 1 review article/meta-analysis (Tsukada 2015), the allele frequency of the c.35delG variant was statistically higher in individuals with hearing loss compared with individuals in the general population. 3.2% (72/2238) of alleles reported in this study harbored 35delG. Compared this to the European population in gnomAD (0.969%) since this is the highest frequency population. Ran a 2x2 contingency table using this data, and the two-tailed P value is <0.0001. PubMed:26969326 Review article / Meta-analysis that looked at ethnic-specific spectrum of GJB2 mutations. 35delG was most prevalent among all the studies included. 52 studies included in this analysis that met the following criteria: 1. The article was published in a peer-reviewed journal in the English language. 2. The prevalence of the GJB2 and SLC26A4 mutation alleles among all individuals with sensorineural hearing loss was used. 3. All exons and frank regions of all hearing loss probands were sequenced. Hearing Loss: Total European (includes Finnish) Alleles tested: 6964 Number of European 35delG alleles: 2556 % of 35delG alleles: 36.7% gnomAD data: Total European + Finnish Alleles: 1419 Number of European + Finnish 35delG alleles: 148927 Variant + Variant - Total Cases 2078 4886 6964 "Controls" 1419 123456 124875 Total 3497 128342 131839 Chi-square with Yates correction Chi squared equals 21034.585 with 1 degrees of freedom. The two-tailed P value is less than 0.0001 The association between rows (groups) and columns (outcomes) is considered to be extremely statistically significant. PubMed:25999548
BA1	✓	Filtering AF calculated from gnomAD data 0.0092 (1207/124552). BA1 can be applied, however this variant is on the HL exclusion list, so the BA1 code will not contribute to the overall pathogenicity.
PVS1	✓	Only 1 coding exon of this gene, LOF variants are well known mechanism for GJB2-related hearing loss
PM3_Very Strong	✓	Over 15 compound hets / homozygotes with other known pathogenic variants in GJB2 reported in Sloan Heggen 2015 (see supplemental table)

Not Met criteria codes

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
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
PS3	✖	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
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✖	Filtering AF calculated from gnomAD data 0.0092 (1207/124552). BA1 can be applied, however this variant is on the HL exclusion list, so the BA1 code will not contribute to the overall pathogenicity.
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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS1	✖	Filtering AF calculated from gnomAD data 0.0092 (1207/124552). BA1 can be applied, however this variant is on the HL exclusion list, so the BA1 code will not contribute to the overall pathogenicity.
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	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

Curation History

Showing 1 to 1 of 1 rows