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_022124.5(CDH23):c.719C>T (p.Pro240Leu)

Version: 1.0

CA253338

4928 (ClinVar)

Gene: CDH23 (HGNC:64072)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal recessive inheritance
UUID: bdc50191-a305-4375-b8cc-89088a4e5cac
Approved on: 2019/7/22
Published on: 2019/10/17

HGVS expressions

NM_022124.5(CDH23):c.719C>T (p.Pro240Leu)
NM_022124.5:c.719C>T
NC_000010.11:g.71570884C>T
CM000672.2:g.71570884C>T
NC_000010.10:g.73330641C>T
CM000672.1:g.73330641C>T
NC_000010.9:g.73000647C>T
NG_008835.1:g.178938C>T
ENST00000224721.12:c.719C>T
ENST00000398809.9:c.719C>T
ENST00000442677.4:c.719C>T
ENST00000466757.8:c.90C>T
ENST00000643732.1:n.495C>T
ENST00000646131.1:c.383C>T
ENST00000224721.10:c.734C>T
ENST00000299366.11:c.719C>T
ENST00000398809.8:c.719C>T
ENST00000398842.7:c.470C>T
ENST00000461841.7:c.719C>T
ENST00000466757.7:c.90C>T
ENST00000616684.4:c.719C>T
ENST00000622827.4:c.719C>T
NM_001171930.1:c.719C>T
NM_001171931.1:c.719C>T
NM_001171932.1:c.719C>T
NM_052836.3:c.719C>T
NM_001171930.2:c.719C>T
NM_001171931.2:c.719C>T
NM_022124.6:c.719C>T
NM_052836.4:c.719C>T
NM_001171932.2:c.719C>T

Pathogenic

Met criteria codes 4

PP1_Strong PM3_Strong PS4 PM2_Supporting

Expert Panel

Hearing Loss VCEP

Not Met criteria codes 2

BP4 PP3

Evidence Links 7

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The allele frequency of the c.719C>T (p.Pro240Leu) variant in the CDH23 gene is 0.05% (10/17246) of East Asian chromosomes by gnomAD, which is a low enough frequency to apply PM2_Supporting based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2_Supporting). This variant has been reported in > 10 probands with hearing loss without evidence of retinal disease, including >5 homozygotes, at least 1 compound heterozygote with c.6712+1G>A variant, and >5 compound heterozygotes with rare variants of uncertain significance (PM3_Strong; PMID:24164807, 24618850, 25963016, 26264712, 17850630, 22899989). This variant has also segregated in 3 siblings with hearing loss (PP1_Strong, PMID: 17850630, 22899989). The variant was identified in the heterozygous state in a patient with Usher syndrome who also harbored a homozygous missense variant in MYO7A (PMID: 24618850). A case-control meta analysis found that the p.Pro240Leu variant was associated with a 12-fold higher risk of hearing loss compared to the wild-type allele (OR = 11.68; 95% CI = 3.16–43.24; PS4), though it should be noted that it appears that some probands were included in more than one study included in the meta-analysis (PMID 30367262). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive hearing loss based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PP1_Strong, PM3_Strong, PM2_Supporting, PS4.

Met criteria codes

PP1_Strong ✔ This variant has also segregated in 3 siblings with hearing loss (PP1_Strong, PMID: 17850630, 22899989).

1 segregation from family #3 PubMed:17850630
2 SEGREGATIONS FROM 2308/2309, 2337/2338. Did not score 2885/2886 from Miyagawa because it is the same family as #3 from Wagasuma. PubMed:22899989

PM3_Strong ✔ 1 point from homozygotes PM3_Strong (3.75 points scored)

Identified heterozygous in three affected siblings who also had a heterozygous PCDH15 variant. PubMed:24164807
Patient with Usher syndrome who had a homozygous missense variant in MYO7A and was also heterozygous for Pro240Leu in CDH23 PubMed:24618850
Probands overlap with Miyagawa 2013. Four families with rare VUS in trans. Scored 1 point total. PubMed:17850630
Pro240Leu Identified in 7 homozygotes and 7 cmp hets. All patients had hearing loss. Fundoscopy performed in 4 probands and was normal. Normal motor milestones. Was not sure if some of these individuals with same variants were related. Also, there is overlap with Wagatsuma 2007. Cmp hets scored conservatively at 1 point. p.P240L / p.R2029W (VUS, 0.017% in EA); p.P240L / p.R2029W; p.P240L / p.E956K; p.P240L / p.E956K; p.P240L / p.E956K; p.P240L / p.E956K; p.P240L / c.6712 + 1G > A; p.P240L / c.6712 + 1G > A; PubMed:25963016
12 probands cmpound het with rare VUS. Patients with phase confirmed reported in Wagatsuma 2007. PubMed:22899989
4 Korean children with profound hearing loss. 2 homozygotes, 2 compound hets. Compound hets: - Patient SH59-133 : p.P240L / p.T1618K (VUS) (linkage performed, but phase does not appear to be confirmed for variants) - Patient

SB56-103: c.C719T; c.8574delC p.P240L;p.Asp2858GlufsX8 phase not confirmed 1.75 points (1 from homozygotes, 0.75 from cmp hets) PubMed:26264712

PS4		✔	A case-control meta analysis found that the p.Pro240Leu variant was associated with a 12-fold higher risk of hearing loss compared to the wild-type allele (OR = 11.68; 95% CI = 3.16–43.24; PS4), though it should be noted that it appears that some probands were included in more than one study included in the meta-analysis (PMID 30367262) Meta-analysis of p.Pro240Leu. Included 4 studies comprising 1624 cases with NSHL and 2793 controls. - Variant allele was associated with 12-fold higher risk of SNHL compared to WT allele (OR = 11.68; 95% CI = 3.16–43.24; Ph = 0.088; I2 = 54.1%, P < 0.001). - PubMed:30367262
PM2_Supporting		✔	0.05% (10/17246) East Asian chromosomes in gnomAD

Not Met criteria codes

BP4		✖	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

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.