

Variant: NM_004086.2(COCH):c.263G>A (p.Gly88Glu)

Version: 2.0

CA253885 [↗](#)

6609 (ClinVar) [↗](#)

Gene: COCH ([HGNC:1690](#))

Condition: nonsyndromic genetic deafness ([MONDO:0019497](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 22c58c35-f743-4a68-82cd-2c83be83263f

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HGVS expressions

NM_004086.2(COCH):c.263G>A (p.Gly88Glu)

NM_004086.2:c.263G>A

NC_000014.9:g.30878834G>A

CM000676.2:g.30878834G>A

NC_000014.8:g.31348040G>A

CM000676.1:g.31348040G>A

NC_000014.7:g.30417791G>A

NG_008211.2:g.9300G>A

ENST00000216361.9:c.458G>A

ENST00000396618.9:c.263G>A

ENST00000555117.2:c.263G>A

ENST00000643575.1:c.263G>A

ENST00000643697.1:n.508G>A

ENST00000644874.2:c.263G>A

ENST00000216361.8:c.263G>A

ENST00000396618.7:c.263G>A

ENST00000460581.6:c.-74G>A

ENST00000475087.5:c.263G>A

ENST00000553772.5:c.239+1106G>A

ENST00000553833.5:n.417G>A

ENST00000555881.5:c.83-1618G>A

ENST00000556908.5:c.215G>A

ENST00000557065.1:c.156-589G>A

NM_001135058.1:c.263G>A

NR_038356.1:n.1618-2282C>T

NM_001347720.1:c.458G>A

NM_004086.3:c.263G>A

NM_001135058.2:c.263G>A

NM_001347720.2:c.458G>A

Pathogenic

Met criteria codes **5**

PP1_Strong

PS3

PP3

PS4_Supporting

PM2_Supporting

Evidence Links **9**

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 2.0](#)
- [PDF](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Hearing Loss VCEP

The NM_004086.3:c.263G>A variant in COCH is a missense variant predicted to cause substitution of Glycine to Glutamic acid at amino acid 88 (p.Gly88Glu). The highest population minor allele frequency in gnomAD v4.1.1 is 0.0006780% (8/1180018 alleles -European [non-Finnish], PM2_Supporting met). The computational predictor REVEL yields a score of 0.933 (PP3 met). The variant has been reported to segregate with progressive, late-onset HL and concomitant vestibular dysfunction in 16 affected family members from 4 families. (PP1_Strong, PS4_Supporting met; PMID: 9806553, 16151339, 25780252, 42195045). Vestibular-evoked potential, distortion product otoacoustic emission and auditory brainstem response measurements as well as histopathology in a knock-in mouse model showed dysfunctional vestibular function, progressive hearing loss, and middle ear granulocytic aggregation. Additionally, immunohistochemical staining showed that G88E protein expression inhibits co-localization with the extracellular matrix of HeLa cells while cell death analysis showed an increase in cytotoxicity in primary fibrocytes. Immunoprecipitation experiments indicated that G88E protein dimerizes with wild-type cochlin and forms agent-resistant oligomers. This was further confirmed by experiments in HEK293 cells showing reduced susceptibility of G88E-containing cochlin to aggrecanase cleavage. Overall, these studies indicate that this variant impacts protein function (PS3 met; PMID: 12843317, 12928864, 18697796, 20228067, 21073934, 25049087, 26256111, 35901072). In summary, based on the current evidence (PP1_Strong, PS3, PM2_Supporting, PP3 & PS4_Supporting), the variant NM_004086.3(COCH):c.263G>A(Gly88Glu) is classified as pathogenic for autosomal dominant non-syndromic SNHL based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP (ClinGen Hearing Loss VCEP specifications version 2; 9/16/2026).

Met criteria codes

PP1_Strong			The variant has been reported to segregate with progressive, late-onset HL and concomitant vestibular dysfunction in 16 affected family members from 4 families. (PMID: 9806553, 16151339, 25780252, 42195045)
PS3			Vestibular-evoked potential, distortion product otoacoustic emission and auditory brainstem response measurements as well as histopathology in a knock-in mouse model showed dysfunctional vestibular function, progressive hearing loss, and middle ear granulocytic aggregation. Additionally, immunohistochemical staining showed that G88E protein expression inhibits co-localization with the extracellular matrix of HeLa cells while cell death analysis showed an increase in cytotoxicity in primary fibrocytes. Immunoprecipitation experiments indicated that G88E protein dimerizes with wild-type cochlin and forms agent-resistant oligomers. This was further confirmed by experiments in HEK293 cells showing reduced susceptibility of G88E-containing cochlin to aggrecanase cleavage. Overall, these studies indicate that this variant impacts protein function

see above	PubMed:25049087 
see above	PubMed:12928864 
see above	PubMed:26256111 
see above	PubMed:12843317 
see above	PubMed:21073934 
see above	PubMed:18697796 
see above	PubMed:34735822 

see above [PubMed:20228067](#) 

see above [PubMed:35901072](#) 

PP3			The computational predictor REVEL yields a score of 0.933.
PS4_Supporting			The variant has been reported in four probands with progressive, late-onset HL and concomitant vestibular dysfunction (PMID: 9806553, 16151339, 25780252, 42195045)
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.1 is 0.0006780% (8/1180018 alleles -European [non-Finnish]).

Curation History

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