

Variant: *NM\_004086.2(COCH):c.355G>A (p.Ala119Thr)*

Version: 1.2

CA253893 [↗](#)

6613 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal dominant inheritance

**UUID:** cb0a2192-d76a-4556-a2d3-b0f2d2569f1e

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### *HGVS expressions*

**NM\_004086.2:c.355G>A**

NM\_004086.2(COCH):c.355G>A (p.Ala119Thr)

NC\_000014.9:g.30878926G>A

CM000676.2:g.30878926G>A

NC\_000014.8:g.31348132G>A

CM000676.1:g.31348132G>A

NC\_000014.7:g.30417883G>A

NG\_008211.2:g.9392G>A

ENST00000216361.9:c.550G>A

ENST00000396618.9:c.355G>A

ENST00000555117.2:c.355G>A

ENST00000643575.1:c.355G>A

ENST00000643697.1:n.600G>A

ENST00000644874.2:c.355G>A

ENST00000216361.8:c.355G>A

ENST00000396618.7:c.355G>A

ENST00000460581.6:c.19G>A

ENST00000475087.5:c.355G>A

ENST00000553772.5:c.239+1198G>A

ENST00000553833.5:n.509G>A

ENST00000555881.5:c.83-1526G>A

ENST00000556908.5:c.307G>A

ENST00000557065.1:c.156-497G>A

NM\_001135058.1:c.355G>A

NR\_038356.1:n.1618-2374C>T

NM\_001347720.1:c.550G>A

NM\_004086.3:c.355G>A

NM\_001135058.2:c.355G>A

NM\_001347720.2:c.550G>A

Uncertain Significance

Met criteria codes **2**

BS3\_Supporting

PM2\_Supporting

Not Met criteria codes **24**

Expert Panel

Hearing Loss VCEP [↗](#)

Criteria Specification Information

[PVS1](#) [PM1](#) [PM3](#) [PM5](#) [PM4](#)  
[PM6](#) [BA1](#) [BS2](#) [BS1](#) [BS4](#)  
[BP4](#) [BP3](#) [BP1](#) [BP2](#) [BP5](#) [BP7](#)  
[PS1](#) [PS2](#) [PS3](#) [PS4](#) [PP1](#) [PP2](#)  
[PP3](#) [PP4](#)

Evidence Links 2



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

Evidence submitted by expert panel

**Hearing Loss VCEP**



The c.355G>A variant in COCH is a missense variant predicted to cause substitution of alanine by threonine at amino acid 119. This variant is absent from gnomAD v2.1.1 (PM2\_Supporting). The computational predictor REVEL gives a score of 0.394, which is neither above nor below the thresholds predicting a damaging or benign impact on COCH function. Functional studies show no differences between wild-type and p.A119T variant cochlin localization and secretion (BS3\_Supporting). While this is not supporting evidence for pathogenicity, other mechanisms of pathogenicity cannot be ruled out. Due to conflicting evidence, this variant is classified as a variant of unknown significance for autosomal dominant nonsyndromic genetic deafness based on the ACMG/AMP criteria applied, as specified by the ClinGen Hearing Loss VCEP: PM2\_P, BS3\_P (Hearing Loss VCEP specifications version 2; 6/15/2022).



**Met criteria codes**



**BS3\_Supporting**   Functional studies show no differences between wild-type and p.A119T variant cochlin localization and secretion. While this not supporting evidence for pathogenicity, other mechanisms of pathogenicity cannot be ruled out.  
 Wild-type cochlin was localized in the ER and compacted in the Golgi complex. Coch protein containing the p.A119T variant was also found to localize in the ER and Golgi complex. Secretion studies showed that the p.A119T mutated protein was detected in the media similarly to wild-type cochlin. [PubMed:25230692](#)



**PM2\_Supporting**   This variant is absent from gnomAD v2.1.1 (PM2\_Supporting).
































**Not Met criteria codes**

**PVS1**   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

**PM3**   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

<b>PM4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PM6</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BA1</b>			The p.Ala119Thr variant is absent from gnomAD. Found in one individual (0.045) in HGVD (Japanese general population).
<b>BS2</b>			Found in one individual (0.045) in HGVD (Japanese general population). But COCH is associated with adult-onset HL, and thus this observation is likely irrelevant.
<b>BS1</b>			The p.Ala119Thr variant is absent from gnomAD. Found in one individual (0.045) in HGVD (Japanese general population).
<b>BS4</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP4</b>			REVEL score does not meet the criteria for BP4 or PP3.
<b>BP3</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP2</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP5</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>BP7</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PS1</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PS2</b>			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PS3</b>			Functional studies show no differences between wild-type and p.A119T variant cochlin localization and secretion. While this not supporting evidence for pathogenicity, other mechanisms of pathogenicity cannot be ruled out.
<b>PS4</b>			Not enough probands to meet PS4_Supporting.

23 Japanese probands with autosomal dominant hearing loss were screened for COCH variants. The p.A119T variant was observed in one individual with a personal and family history suggestive of autosomal dominantly inherited hearing loss and vestibular dysfunction. The variant was not observed in 4 unaffected family members. Edited by Alex C (3/30/2018). [PubMed:14512963](#)

<b>PP1</b>	 	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PP2</b>		No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
<b>PP3</b>	 	REVEL score does not meet the criteria for BP4 or PP3.
<b>PP4</b>	 	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

#### Curation History [↗](#)

Showing 1 to 4 of 4 rows

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