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Variant: NM_004086.2(COCH):c.151C>T (p.Pro51Ser)

CA253889

6611 (ClinVar)

Gene: COCH (HGNC:1690)
Condition: nonsyndromic genetic deafness (MONDO:0019497)
Inheritance Mode: Autosomal dominant inheritance
UUID: d4782d4a-27b7-4626-acc7-f8758d33384d
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HGVS expressions

NM_004086.2:c.151C>T
NM_004086.2(COCH):c.151C>T (p.Pro51Ser)
NC_000014.9:g.30877640C>T
CM000676.2:g.30877640C>T
NC_000014.8:g.31346846C>T
CM000676.1:g.31346846C>T
NC_000014.7:g.30416597C>T
NG_008211.2:g.8106C>T
NM_001135058.1:c.151C>T
NR_038356.1:n.1618-1088G>A
NM_001347720.1:c.346C>T
NM_004086.3:c.151C>T
ENST00000216361.8:c.151C>T
ENST00000396618.7:c.151C>T
ENST00000460581.6:c.-186C>T
ENST00000475087.5:c.151C>T
ENST00000553772.5:c.151C>T
ENST00000553833.5:n.305C>T
ENST00000555881.5:c.82+2537C>T
ENST00000556908.5:c.103C>T
ENST00000557065.1:n.67C>T

Pathogenic

Met criteria codes 4

PP1_Strong PS4 PM2 PP3

Not Met criteria codes 19

PVS1 BS1 BS4 BS2 BP7
BP5 BP4 BP3 BP2 PS1 PS3
PS2 BA1 PM5 PM4 PM1
PM3 PM6 PP4

Evidence Links 10

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The c.151C>T (p.Pro51Ser) variant in COCH has been reported to segregate with late onset progressive hearing loss and vestibular dysfunction in > 25 family members (PP1_S; PMID: 9931344, 11332404). The variant meets PM2 and has been observed in at least 15 affected probands (PS4, PMID: 28733840, 16151338, 11332404). The allele frequency of the p.Pro51Ser variant is 0.001% (1/111716) of European chromosomes by the Genome Aggregation Database (http://gnomad.broadinstitute.org), which is a low enough frequency to award PM2 based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal dominant hearing loss (PM2). Computational prediction tools and conservation analysis suggest that the p.Pro51Ser variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant hearing loss based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PP1_S, PS4, PM2, PP3.

Met criteria codes

PP1_Strong ✔

The Dutch family in de Kok 1999 alone meets the criteria for segregation evidence of PP1_Strong. It is noted that no evidence of non-penetrance was observed based on the 22 members that they sequenced.

Eight of nine subjects with the same P51S variant in COCH had similar rediologic lesions indicating focal sclerosis of one or more semiciruclar canals. The patients all had hearing loss and vestibular involvement consistent with DFNA9. The authors assert that this is a new phenotype associated with the variant/COCH gene. PubMed:24662630

Dutch family with AD nonsyndromic progressive sensorineural heraing loss and vestibular involvement. This family had a later age of onset than a previous DFNA9 family. Family W98-011 comprises >200 members 22 of which were genetically analyzed. AD inheritance with no evidence of non-penetrance in the pedigree. Identified 12 affected and 4 "probably affected members of the nuclear family" who were sequenced. This meets criteria for PP1_Strong. PubMed:9931344

Large Dutch family with HL and vestibular involvement segregating with variant. 44 affected family members. 30 participated in the study. PubMed:16151338

PS4 ✔

Decided to use PS4 because there were at least 12 probands with the variant and only one individual in gnomAd therefore we can use PS4 However, this is an instance where the hearing loss is progressive and late onset and therefore it is highly probable that that individual just has a mild case of HL or will develop it later on.

Identified an Austrian family with AD segregating progressive late onset hearing loss who had WES identifiy the c.151C>T missense (p.Pro51Ser) variant. The family consists of 4 generations. PubMed:28733840

Identified a new Dutc family with progressive hearing loss and vestibular impairment. The family was also found to have the p.Pro51Ser variant segregating with disease. They found that hearing started to deteriorate in all mutation carriers around 43 years of age onwards. Vestibular dysfunction started around age 34. PubMed:16151338

This study identified 10 familes with the same haplotype who carried the P51S and had it segregate with disease in their families.The families were all Dutch or Belgian. They concluded that these families must have a common ancestor. PubMed:11332404

PM2 ✔

This variant is present in 1/111716 European alleles. This frequency meets our PM2 threshold for AD hearing loss

PP3 ✔

REVEL score of 0.873

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	This variant is present in 1/111716 European alleles. This frequency meets our PM2 threshold for AD hearing loss
BS4	✖	Eight of nine subjects with the same P51S variant in COCH had similar rediologic lesions indicating focal sclerosis of one or more semiciruclar canals. The patients all had hearing loss and vestibular involvement consistent with DFNA9. The authors assert that this is a new phenotype associated with the variant/COCH gene. PubMed:24662630 Dutch family with AD nonsyndromic progressive sensorineural heraing loss and vestibular involvement. This family had a later age of onset than a previous DFNA9 family. Family W98-011 comprises >200 members 22 of which were genetically analyzed. AD inheritance with no evidence of non-penetrance in the pedigree. Identified 12 affected and 4 "probably affected members of the nuclear family" who were sequenced. This meets criteria for PP1_Strong. PubMed:9931344 Large Dutch family with HL and vestibular involvement segregating with variant. 44 affected family members. 30 participated in the study. PubMed:16151338
BS2	✖	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
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	REVEL score of 0.873
BP3	✖	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
PS1	✖	position in ClinVar is a synonymous c.153A>C variant
PS3	✖	There are conflicting reports indicating the functional impact of the variant. Some say that the variant impedes secretion however, the most recent study conducted by Bae et al. 2014 found that it did not. This study showed that all the variants localized in the peri-nuclear Gogli region but that the p.P51S variants showed signfiicant staining within the Golgi complex similar to WT cochlin. The p.P51S variant also showed extreacellular deposition that slightly co-localized with fibronectin. They concluded that the extracellular deposits are indistinguishable form WT cochlin and yet since they cause the same histopathoglogy as the other mutants, it is likely that they are unable to interact with the ECM components. This should not be counted towards pathogenicity. PubMed:12928864

The variant was found not to impede secretion in this study dispite previous reports indicating that it may. (Grabski 2003, Robertson 2003, Street 2005, and Yao 2010 are all cited). PubMed:25230692

Investigated cochlins containing p.P51S as well as p.V66G, p.G88E, p.I109T, p.W117R, plV123E, and p.C162Y variants. Found that all variants demonstrate reduced cleavage by aggrecanase. This suggestes that the impaired post-translational cleavage by aggrecanase may be a mechanism underlying the disease. See figure 3. PubMed:26256111

This study investigated the inner ear tissues from a post Mortem sample obtained from a member of a DFNA9 Dutch family with a segregating p.P51S variant, They compared the bone sampels to WT and -/- COCH mice. They also conducted expression studies. They found that the p.P51S variant had stable expression of COCH and therefore does not cause loss of the protein. There is no evidence directly implicating the variant but it does support the COCH gene's role in disease. PubMed:16481359

This study found that the P51S variant and found that this variant was one of the mutants that showed a varying degreee of increase in the levels of full-length cochlin and decreases in the levels of processed forms PubMed:20228067

PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	This variant is present in 1/111716 European alleles. This frequency meets our PM2 threshold for AD hearing loss
PM5	✖	Only other variant identified at this position in ClinVar is a synonymous c.153A>C variant
PM4	✖	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
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	All of the family cases are highly specific for the late onset progressive hearing loss with vestibular involvement. This variant has been shown to be a founder variant in Dutch/Belgian populations and has also been seen in an Austrian family. After review, expert panel decided not to apply PP4. This study shows several Dutch/Belgian families with the variant segregating with a highly specific disease phenotype. ie. age of onset and severity of HL and vestibular dysfunction. PubMed:11332404

Curation History

Showing 1 to 1 of 1 rows

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