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Variant: NM_206933.2(USH2A):c.2276G>T (p.Cys759Phe)

Version: 1.0

CA252233

2356 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3b9c6310-7e67-431a-a1be-4962b9e7f495
Approved on: 2019/7/28
Published on: 2019/8/16

HGVS expressions

NM_206933.2:c.2276G>T
NM_206933.2(USH2A):c.2276G>T (p.Cys759Phe)
NC_000001.11:g.216247118C>A
CM000663.2:g.216247118C>A
NC_000001.10:g.216420460C>A
CM000663.1:g.216420460C>A
NC_000001.9:g.214487083C>A
NG_009497.1:g.181279G>T
NG_009497.2:g.181331G>T
ENST00000307340.8:c.2276G>T
ENST00000674083.1:c.2276G>T
ENST00000307340.7:c.2276G>T
ENST00000366942.3:c.2276G>T
NM_007123.5:c.2276G>T
NM_206933.3:c.2276G>T
NM_007123.6:c.2276G>T
NM_206933.4:c.2276G>T

Pathogenic

Met criteria codes 6

PM3_Strong PP1_Strong PS4 PP3 PP4 BS1

Not Met criteria codes 20

PS1 PS2 PS3 BP4 BP3 BP1 BP2 BP5 BP7 PP2 BA1 PM1 PM5 PM4 PM6 PM2 BS2 PVS1 BS4 BS3

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Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The p.Cys759Phe variant in USH2A has been reported in 10 individuals with a clinical diagnosis of Usher Syndrome type II who were all confirmed compound heterozygous with a second pathogenic variant on the remaining allele (PMIDs: 16098008, 24944099, 29912909) (PM3_Strong). Note that scoring for PM3 was downgraded from PM3_VeryStrong to PM3_Strong since this variant has an allele frequency that meets criteria for BS1 (see below). Co-segregation with Usher II was demonstrated collectively in 2 affected and 13 unaffected siblings (LOD score: 2.23). When including all families affected with Usher II or an atypical Usher presentation (retinitis pigmentosa (RP) with some form of hearing loss), co-segregation can be identified in three affected and 26 unaffected siblings total (LOD score: 4.45) (PMID: 29912909) (PP1_Strong). When considering those patients who present with isolated RP, the variant segregated in an additional 15 affected and 32 unaffected siblings (LOD score: 12.43) (PMIDs:10775529, 12525556, 21151602, 29912909). The filtering allele frequency (the lower threshold of the 95% CI of 72/35410) of the p.Cys759Phe variant in the Latino population in gnomAD is 0.17% and it has also been observed at the filtering allele frequency (the lower threshold of the 95% CI of 17/2536) of 0.43% across several Spanish or Latino populations published in the literature (PMIDs: 12525556, 12112664, 25262649, 26764160, 25261458, 25823529; BS1). Although this allele frequency meets the threshold defined by the ClinGen Hearing Loss Expert Panel for considering strong evidence against pathogenicity for autosomal recessive hearing loss variants, other studies suggest it may still be associated with Usher syndrome, albeit with potentially reduced penetrance. The variant is statistically enriched in cohorts of Usher (2.00% (54/2704) in Usher patients compared to 0.67% (17/2536) as the highest and most ethnically matched published Spanish and Latino control populations; Fisher's exact p value <0.0001) and RP patients (1.87% (109/5828) in RP patients compared to 0.71% in published Spanish and Latino controls; Chi-Square p value <0.0001) (PMIDs: 12525556, 12112664, 25262649, 26764160, 25261458, 25823529, 10909849, 12112664, 14970843, 15325563, 16098008, 17405132, 18273898, 19683999, 22004887, 21738395, 24944099, 25375654, 28041643, 29588463, 21151602, 25097241, 23591405, 25910913, 25649381, 29283788, 22135276, 22334370) (PS4). The association with Usher syndrome is particularly clear when paired with a predicted loss-of-function or other pathogenic variant compared to homozygous individuals who are more at risk to develop non-syndromic RP (PMIDs: 29912909 and 25375654). There may also be evidence of reduced penetrance for both hearing loss and RP as two homozygous individuals were documented to have no evidence of any phenotype through their 6th decade (PMIDs: 16098008, 12525556). The PP4 rule has also been applied to this variant given the combination of hearing loss and RP that is seen in these patients and that most patients were screened for other Usher genes. Lastly, computational prediction tools and conservation analysis suggest that the p.Cys759Phe variant may impact the protein (REVEL: 0.902), and an analysis using the homologous mouse laminin gamma 1 chain concluded that this variant is likely to disrupt disulfide bonding with the cysteine at position 747 (PMID: 10909849) (PP3). In summary, the ClinGen Hearing Loss Expert Panel believes that the evidence for the pathogenicity of this variant for Usher Syndrome outweighs its higher than expected allele frequency in population databases and other general population cohorts. Therefore, the BS1 code will not contribute to the overall classification. In summary, this variant meets criteria to be classified as pathogenic for Usher syndrome (ACMG codes applied: BS1, PS4, PM3_Strong, PP1_Strong, PP4, and PP3). Please note that patients with this variant may present with either Usher syndrome or with isolated RP. Isolated RP presentations are more common when the variant is seen in homozygosity as opposed to combined with a distinct pathogenic USH2A variant.

Met criteria codes

PM3_Strong	✔	Multiple of observations of p.Cys759Phe in trans with various other variants in Usher II patients (15.5 total points; max is 4). However, because BS1 has been met, I have subtracted 2 points (2 points = PM3_Strong).
PP1_Strong	✔	Strong LOD score for association with retinitis pigmentosa (RP; LOD = 20.62) and Usher Syndrome (LOD = 4.45, counting full Usher and Atypical Usher)
PS4	✔	Compared allele variant and wild-type allele counts using Chi-square (or Fisher's exact, when applicable) using 4 combinations: ARRP and Usher syndrome (including atypical) cases, and compared to either all controls or just Spanish cohorts. All were statistically significant with all p values less than or equal to 0.0001
PP3	✔	REVEL score is >0.7 (0.902)
PP4	✔	Associated with atypical usher syndrome and non-syndromic retinitis pigmentosa (in addition to Usher Syndrome II).

BS1		✔	Found at an allele frequency of 0.33% (21/4278 with a 95% CI) in meta-cohort of healthy individuals. It has also been observed at 0.43% (95% CI of 17/2536) of across several Spanish or Latino populations published in the literature. GnomAD Latino = 0.17% (95% CI of 72/35410). Found on 0.78% (4/504) of health Spanish control chromosomes. PubMed:25261458 Variant found in 0.75% (3/400) of "ethnically matched" control chromosomes. PubMed:25823529 Classified as "Benign" based on maximum MAF in subpopulations in Otoscope/Iowa database (0.63%). However, as of 10/10/2018, the listing in the DVD has this variant as a VUS (manual curation), with a population frequency of 0.62% (2/320) in the Colombian population and 0.55% (2/360) in the Spanish from Almería and Granada population. http://deafnessvariationdatabase.org/variant/88547?full PubMed:25262649 Found on 0.72% (4/552) of Spanish chromosomes with no known diseases. PubMed:26764160

Not Met criteria codes

PS1		✖	No other variants reported at this codon
PS2		✖	No de novo observations
PS3		✖	No functional studies have been conducted.
BP4		✖	REVEL score is >0.7 (0.902)
BP3		✖	not an in-frame insertion or deletion.
BP1		✖	Neither are applicable for hearing loss genes
BP2		✖	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
BP7		✖	not a silent variant
PP2		✖	Neither are applicable for hearing loss genes
BA1		✖	Found at an allele frequency of 0.33% (21/4278 with a 95% CI) in meta-cohort of healthy individuals. Or using the studies below: 0.43% (17/2536 with a 95% CI)
PM1		✖	Not applicable for USH2A
PM5		✖	No other variants reported at this codon

PM4		✖	not an in-frame insertion or deletion.
PM6		✖	No de novo observations
PM2		✖	Found at an allele frequency of 0.33% (21/4278 with a 95% CI) in meta-cohort of healthy individuals. Or using the studies below: 0.43% (17/2536 with a 95% CI)
BS2		✖	Found in two healthy adults, aged 44 and 45. No evidence of hearing loss or RP. Not applying this evidence because variant is associated with late onset or absent hearing loss. See Bernal 2005 and Pozo 2015 papers.
PVS1		✖	Not a truncating variant
BS4		✖	Variant found as a homozygote in two siblings from a consanguineous family (S-23) reported in Bernal et al (2003). Neither homozygous individual presented with symptoms, and two other siblings, both affected with retinitis pigmentosa, were found to be heterozygotes. Follow-analysis in Pozo et al (2015) found that both affected individuals were homozygous for a variant in PDE6B (p.Arg560Cys), whereas the two unaffected USH2A (p.Cys759Phe) homozygotes were heterozygous for PDE6B (p.Arg560Cys). See supplementary figure 1 of Pozo (2015). Code not applied because late-onset.
BS3		✖	No functional studies have been conducted.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_206933.2(USH2A):c.2276G>T (p.C...	Pathogenic	Usher Syndrome	2019-08-16	1.0	-	USH2A

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