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Variant: NM_206933.2(USH2A):c.5581G>A (p.Gly1861Ser)

CA262105

48535 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 16f373e0-f3cf-4ebe-91ea-6d1a22e44f9c
Approved on: 2018-09-14
Published on: 2018-12-10

HGVS expressions

NM_206933.2(USH2A):c.5581G>A (p.Gly1861Ser)
NM_206933.2:c.5581G>A
NC_000001.11:g.216073292C>T
CM000663.2:g.216073292C>T
NC_000001.10:g.216246634C>T
CM000663.1:g.216246634C>T
NC_000001.9:g.214313257C>T
NG_009497.1:g.355105G>A
NR_125992.1:n.136+692C>T
NR_125993.1:n.136+692C>T
NM_206933.3:c.5581G>A
ENST00000307340.7:c.5581G>A

Pathogenic

Met criteria codes 6

PM3_Strong PS4 PP3 PP1 PP4 PM2_Supporting

Not Met criteria codes 17

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

Evidence Links 4

Expert Panel

Hearing Loss VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hearing Loss VCEP

The allele frequency of the p.Gly1861Ser variant in USH2A is 0.017% (3/17184) of East Asian chromosomes by the Genome Aggregation Database (http://gnomad.broadinstitute.org), which is a low enough frequency to award PM2_Supporting based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2_P). This variant was found to have a statistically higher prevalence in affected individuals over controls (PS4; PMIDs: 26310143, 26338283, 23737954, Partners LMM internal data SCV000065557.5). This variant has been detected in 4 patients with hearing loss in trans with pathogenic or suspected-pathogenic

variants (PM3_S; PMIDs: 26310143, 26338283, 23737954, Partners LMM internal data SCV000065557.5). The variant has been reported to segregate with hearing loss in one affected family member (PP1, PMID: 26310143). At least one patient with a variant in this gene displayed features of mild to severe hearing loss and retinitis pigmentosa (PP4; PMID: PMIDs: 26310143, 26338283, 23737954, Partners LMM internal data SCV000065557.5). Computational prediction tools and conservation analysis suggest that the p.Gly1861Ser variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive Usher syndrome based on the ACMG/AMP criteria applied, as specified by the Hearing Loss Expert Panel: PS4, PM2_P, PP3, PM3_S, PP1, PP4.

Met criteria codes

PM3_Strong ✔

I gave 1 point for the splicing variant in trans, 1 point for the nonsense variant, and 0.5 for two of the missense variants= 2.5 pts There is also an LMM case that has the same -2 splice variant as Jiang et al, but this would still not bump up to VS.

67 Chinese families with Usher syndrome were tested for variants in 196 retinal disease genes. The p.Gly1861Ser variant was identified 1 patient with c.8559-2A>G in trans. PubMed:26338283
This is a case report of a Chinese family with pseudo-dominant Usher syndrome. The proband is compound het for p.Gly1861Ser and p.C934W. There is also an affected brother who has this genotype. PubMed:26310143
5 unrelated Chinese families with Usher syndrome were tested using a panel of 144 known genes for deep exome resequencing. The p.Gly1861Ser variant was identified in family F2 in trans with a novel frameshift c.8602delA, but was in cis with a second missense variant p.R5143C. The cis variants were also present in an unaffected sib. PubMed:23737954
179 unrelated Chinese patients with inherited retinal dystrophy were tested for variants in 164 known genes. The p.Gly1861Ser variant was identified in 2 patients with Usher syndrome. The patients were compound het for p.G1526R and p.R5143C, respectively. I hesitate to count the patient with the p.R5143C variant in trans because this is the same author that identified that variant in cis in a patient. NOTE: p.R5143C is benign due to a MAF OF 0.9% in East Asians, and based on Huang 2013, variants likely in cis. Did not count proband with this variant (Andrea) PubMed:25356976

PS4 ✔

Cases: 5/504 Asian alleles gnomAD: 3/17184 Asian alleles Chi-square with Yates correction: Chi squared equals 82.448 with 1 degrees of freedom. The two-tailed P value is less than 0.0001.The association between rows (groups) and columns (outcomes) is considered to be extremely statistically significant.

PP3 ✔

Our cutoff is >0.7 and the variant is 0.786, so PP3 is met. No splicing impact is predicted.

PP1 ✔

The proband and 1 affected sib carry this variant.

This is a case report of a Chinese family with pseudo-dominant Usher syndrome. The proband is compound het for p.Gly1861Ser and p.C934W. There is also an affected brother who has this genotype. PubMed:26310143

PP4 ✔

Many of the reported patients had Usher syndrome and were negative for variants in other Usher syndrome genes.

PM2_Supporting ✔

Variant is too frequent to meet PM2_supporting. -ANDREA: disagree; meets PM2 supporting, since it is at 0.017% of East Asian chroms and cutoff is 0.07%.

Not Met criteria codes

PM6 ✖

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
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
BA1	✖	Variant is too frequent to meet PM2_supporting. -ANDREA: disagree; meets PM2 supporting, since it is at 0.017% of East Asian chroms and cutoff is 0.07%.
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	Variant is too frequent to meet PM2_supporting. -ANDREA: disagree; meets PM2 supporting, since it is at 0.017% of East Asian chroms and cutoff is 0.07%.
BS4	✖	This is a case report of a Chinese family with pseudo-dominant Usher syndrome. The proband is compound het for p.Gly1861Ser and p.C934W. There is also an affected brother who has this genotype. PubMed:26310143
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	✖	Our cutoff is >0.7 and the variant is 0.786, so PP3 is met. No splicing impact is predicted.
BP2	✖	67 Chinese families with Usher syndrome were tested for variants in 196 retinal disease genes. The p.Gly1861Ser variant was identified 1 patient with c.8559-2A>G in trans. PubMed:26338283 This is a case report of a Chinese family with pseudo-dominant Usher syndrome. The proband is compound het for p.Gly1861Ser and p.C934W. There is also an affected brother who has this genotype. PubMed:26310143 5 unrelated Chinese families with Usher syndrome were tested using a panel of 144 known genes for deep exome resequencing. The p.Gly1861Ser variant was identified in family F2 in trans with a novel frameshift c.8602delA, but was in cis with a second missense variant p.R5143C. The cis variants were also present in an unaffected sib. PubMed:23737954 179 unrelated Chinese patients with inherited retinal dystrophy were tested for variants in 164 known genes. The p.Gly1861Ser variant was identified in 2 patients with Usher syndrome. The patients were compound het for p.G1526R and p.R5143C, respectively. I hesitate to count the patient with the p.R5143C variant in trans because this is the same author that identified that variant in cis in a patient. NOTE: p.R5143C is benign due to a MAF OF 0.9% in East Asians, and based on Huang 2013, variants likely in cis. Did not count proband with this variant (Andrea) PubMed:25356976

BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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