The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_206933.2(USH2A):c.1036A>C (p.Asn346His)

CA262054

48347 (ClinVar)

Gene: USH2A (HGNC:7399)
Condition: Usher syndrome (MONDO:0019501)
Inheritance Mode: Autosomal recessive inheritance
UUID: 211c3a9c-3789-42d9-ab55-04892c95f534
Approved on: 2018-09-14
Published on: 2018-12-10

HGVS expressions

NM_206933.2:c.1036A>C
NM_206933.2(USH2A):c.1036A>C (p.Asn346His)
NC_000001.11:g.216325412T>G
CM000663.2:g.216325412T>G
NC_000001.10:g.216498754T>G
CM000663.1:g.216498754T>G
NC_000001.9:g.214565377T>G
NG_009497.1:g.102985A>C
NM_007123.5:c.1036A>C
NM_206933.3:c.1036A>C
ENST00000307340.7:c.1036A>C
ENST00000366942.3:c.1036A>C

Pathogenic

Met criteria codes 5

PP4 PP3 PM3_Very Strong PM2_Supporting PP1_Strong

Not Met criteria codes 18

PS4 PS2 PS1 PS3 PM5 PM1 PM4 PM6 BA1 BS2 PVS1 BS1 BS4 BP5 BP7 BP2 BP4 BP3

Evidence Links 7

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.Asn346His variant in the USH2A gene is 0.016% (20/126318) of European (Non-Finnish) 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 Usher syndrome (PM2_Supporting). The p.Asn346His variant in USH2A has been reported to segregate with hearing loss in at least 7 families including 13 family members (PP1_S; 10729113, 15241801, 17405132, 25521520, 24160897, 22135276). This variant has been detected in patients with hearing loss in trans

with at least 4 pathogenic or suspected-pathogenic variants (PM3_VS; PMID: 15241801, 24160897, 22135276, 26969326). At least one patient with a variant in this gene displayed features of mild to severe hearing loss and retinitis pigmentosa (PP4; PMID: 10729113, 15241801, 17405132, 25521520, 24160897, 22135276). Computational prediction tools and conservation analysis suggest that the p.Asn346His 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: PM2_Supporting, PP1_S, PM3_VS, PP4, PP3.

Met criteria codes

PP4 ✔

The patiens of compound heterozygotes or homozygotes with the mutation showed retinitis pigmentosa with hearing loss. Enough patients were also tested for the other Usher syndrome genes and found to be negative for changes in them. I also agree. -MD

The Asn346His variant was identified in 1 proband in combination with a second loss of function allele c.1227G>A (p.Trp409X). PubMed:15241801
1 compound het proband with Arg1295X on remaining allele. Variants segregated in 3 affected relatives. 1 homozygous proband, variant segregated in 2 affected relatives. PubMed:24160897
Asn346His variant was identified in 1 proband with USH2, compound heterozygous with Gly4403fs variant PubMed:17405132
The Asn346His variant was identified in 2 probands with USH2. It was observed in a large Swedish family with Arg1295X, but the two variants were not present in the same individuals. In an American family, it was compound heterozygous with another pathogenic variant 2299delG (Glu767fs). The cDNA coordinate (c.1042A>C = p.348) in this paper was wrong, but the alignment figure showed the variant matching N346H. PubMed:10729113
Usher syndrome type II PubMed:22135276
Two siblings were cmp het for this variant and Thr4439Ile. The brother had Usher syndrome. The 43 year old sister had hearing loss and a slightly abnormal finding on ERG, but was otherwise normal. PubMed:25521520

PP3 ✔

Agree. REVEL is >0.7 -MD

PM3_Very Strong ✔

This could actually be upgraded to PM3_very strong. There are >4 cases of this variant being identified in trans with a known pathogenic variant. I've added more publications below. -MD

detected in trans with p.Trp409X PubMed:15241801
detected in trans with p.R1295X PubMed:24160897
detected in trans with c.2299del PubMed:26969326
detected in trans with p.Glu3305ArgfsX41, p.Trp3521Arg, and Lys419Phe PubMed:22135276

PM2_Supporting ✔

I agree. Variant is present in (20/126318)) 0.00015% Europeans in gnomAD. -MD

PP1_Strong ✔

Cosegretation with the phenotype were observed in at least 7 families including 13 affected members. Agree with this code usage. MD

The Asn346His variant was identified in 1 proband in combination with a second loss of function allele c.1227G>A (p.Trp409X) PubMed:15241801
1 compound het proband with Arg1295X on remaining allele. Variants segregated in 3 affected relatives. 1 homozygous proband, variant segregated in 2 affected relatives. PubMed:24160897
The Asn346His variant was identified in 2 probands with USH2. It was observed in a large Swedish family with Arg1295X, but the two variants were not present in the same individuals. In an American family, it was compound

heterozygous with another pathogenic variant 2299delG (Glu767fs). The cDNA coordinate (c.1042A>C = p.348) in this paper was wrong, but the alignment figure showed the variant matching N346H. PubMed:10729113
Asn346His variant was identified in 1 proband with USH2, compound heterozygous with Gly4403fs variant PubMed:17405132
Four compound hets reported; variants on remaining allele were Thr4439Ile, Glu3305fs, Trp3521Arg, Cys419Phe. One individual was het only. PubMed:22135276
Two siblings were cmp het for this variant and Thr4439Ile. The brother had Usher syndrome. The 43 year old sister had hearing loss and a slightly abnormal finding on ERG, but was otherwise normal. PubMed:25521520

Not Met criteria codes

PS4	✖	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
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
PM5	✖	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
PM4	✖	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
BA1	✖	I agree. Variant is present in (20/126318)) 0.00015% Europeans in gnomAD. -MD
BS2	✖	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
BS1	✖	I agree. Variant is present in (20/126318)) 0.00015% Europeans in gnomAD. -MD

BS4			The Asn346His variant was identified in 1 proband in combination with a second loss of function allele c.1227G>A (p.Trp409X) PubMed:15241801 1 compound het proband with Arg1295X on remaining allele. Variants segregated in 3 affected relatives. 1 homozygous proband, variant segregated in 2 affected relatives. PubMed:24160897 The Asn346His variant was identified in 2 probands with USH2. It was observed in a large Swedish family with Arg1295X, but the two variants were not present in the same individuals. In an American family, it was compound heterozygous with another pathogenic variant 2299delG (Glu767fs). The cDNA coordinate (c.1042A>C = p.348) in this paper was wrong, but the alignment figure showed the variant matching N346H. PubMed:10729113 Asn346His variant was identified in 1 proband with USH2, compound heterozygous with Gly4403fs variant PubMed:17405132 Four compound hets reported; variants on remaining allele were Thr4439Ile, Glu3305fs, Trp3521Arg, Cys419Phe. One individual was het only. PubMed:22135276 Two siblings were cmp het for this variant and Thr4439Ile. The brother had Usher syndrome. The 43 year old sister had hearing loss and a slightly abnormal finding on ERG, but was otherwise normal. PubMed:25521520
BP5			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
BP2			detected in trans with p.Trp409X PubMed:15241801 detected in trans with p.R1295X PubMed:24160897 detected in trans with c.2299del PubMed:26969326 detected in trans with p.Glu3305ArgfsX41, p.Trp3521Arg, and Lys419Phe PubMed:22135276
BP4			Agree. REVEL is >0.7 -MD
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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