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Variant: NM_130838.1(UBE3A):c.317C>A (p.Thr106Lys)

Version: 1.0

CA333390

155994 (ClinVar)

Gene: UBE3A (HGNC:7337)
Condition: Angelman syndrome (MONDO:0007113)
Inheritance Mode: Autosomal dominant inheritance (with paternal imprinting (HP:0012274))
UUID: ab249ad8-9000-4fe3-b765-33904af0119f
Approved on: 2021/3/26
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HGVS expressions

NM_130838.1(UBE3A):c.317C>A (p.Thr106Lys)
NM_130838.1:c.317C>A
NC_000015.10:g.25371797G>T
CM000677.2:g.25371797G>T
NC_000015.9:g.25616944G>T
CM000677.1:g.25616944G>T
NC_000015.8:g.23168037G>T
NG_009268.1:g.72185C>A
ENST00000438097.6:c.317C>A
ENST00000625778.3:c.317C>A
ENST00000635914.1:c.317C>A
ENST00000637886.1:c.377C>A
ENST00000638011.1:c.317C>A
ENST00000638155.1:c.317C>A
ENST00000648336.2:c.377C>A
ENST00000649550.1:c.317C>A
ENST00000650110.1:c.386C>A
ENST00000675000.1:n.1052C>A
ENST00000675177.1:c.200C>A
ENST00000675593.1:n.3073C>A
ENST00000232165.7:c.317C>A
ENST00000397954.6:c.386C>A
ENST00000428984.6:c.317C>A
ENST00000438097.5:c.317C>A
ENST00000566215.5:c.317C>A
ENST00000614096.4:c.377C>A
ENST00000625778.2:c.317C>A
ENST00000626068.2:c.398C>A
ENST00000626793.2:n.428C>A
ENST00000628733.2:c.377C>A
ENST00000630424.2:c.317C>A
ENST00000630907.2:c.377C>A
NM_000462.3:c.386C>A
NM_130839.2:c.377C>A
NM_000462.5:c.386C>A
NM_001354505.1:c.377C>A
NM_001354506.1:c.317C>A

NM_001354507.1:c.317C>A
NM_001354508.1:c.317C>A
NM_001354509.1:c.317C>A
NM_001354511.1:c.317C>A
NM_001354512.1:c.317C>A
NM_001354513.1:c.317C>A
NM_001354523.1:c.317C>A
NM_001354526.1:c.317C>A
NM_001354538.1:c.377C>A
NM_001354539.1:c.317C>A
NM_001354540.1:c.317C>A
NM_001354541.1:c.317C>A
NM_001354542.1:c.317C>A
NM_001354543.1:c.317C>A
NM_001354544.1:c.317C>A
NM_001354545.1:c.377C>A
NM_001354546.1:c.200C>A
NM_001354547.1:c.317C>A
NM_001354548.1:c.317C>A
NM_001354549.1:c.317C>A
NM_001354550.1:c.361+3668C>A
NM_001354551.1:c.301+3668C>A
NM_130838.3:c.317C>A
NM_130839.4:c.377C>A
NR_146177.1:n.18393-19799G>T
NR_148916.1:n.925C>A
NM_001354506.2:c.317C>A
NM_001354507.2:c.317C>A
NM_001354508.2:c.317C>A
NM_001354509.2:c.317C>A
NM_001354511.2:c.317C>A
NM_001354512.2:c.317C>A
NM_001354513.2:c.317C>A
NM_001354523.2:c.317C>A
NM_001354538.2:c.377C>A
NM_001354539.2:c.317C>A
NM_001354540.2:c.317C>A
NM_001354541.2:c.317C>A
NM_001354542.2:c.317C>A
NM_001354543.2:c.317C>A
NM_001354544.2:c.317C>A
NM_001354545.2:c.377C>A
NM_001354546.2:c.200C>A
NM_001354547.2:c.317C>A
NM_001354548.2:c.317C>A
NM_001354549.2:c.317C>A
NM_001354550.2:c.361+3668C>A
NM_001354551.2:c.301+3668C>A
NM_001374461.1:c.317C>A
NM_130838.4:c.317C>A
NM_130839.5:c.377C>A
NR_148916.2:n.893C>A

Pathogenic

Met criteria codes 6

PS4_Supporting | PP3 | PM5 | PP1_Strong | PM2_Supporting | PS3_Supporting

Evidence Links 2

Expert Panel

Rett and Angelman-like Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The variant has been reported to segregate in at least five informative meioses (PMID 25212744, internal database) (PP1_Strong). A pathogenic missense variant (p.Thr106Pro) has been previously identified within this codon which indicates that this residue is critical to the function of the protein (PMID 15054837) (PM5). Protein expression analysis in transfected cell lines has shown that this variant reduces protein function (PMID 26255772) PS3_Supporting). The p.Thr106Lys variant has been observed in at least 1 other individual with Angelman syndrome (PMID 25212744) (PS4_Supporting). The p.Thr106Lys variant in UBE3A is absent from gnomAD (PM2_Supporting). Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3). In summary, the p.Thr106Lys variant in UBE3A is classified as pathogenic for Angelman syndrome based on the ACMG/AMP criteria (PP1_strong, PM5, PS3_supporting, PS4_supporting, PM2_supporting, PP3).

Met criteria codes

PS4_Supporting	✓	The p.Thr106Lys variant has been observed in at least 1 other individual with Angelman syndrome (PMID 25212744) Review of UBE3A variants identified in a cohort of 2515 AS patients. Variant was identified identified in one proband, found to be maternally inherited, and was present in proband's affected sister and in two affected maternal cousins. PubMed:25212744
PP3	✓	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own
PM5	✓	A pathogenic missense variant (p.Thr106Pro) has been previously identified within this codon which indicates that this residue is critical to the function of the protein (PMID 15054837)
PP1_Strong	✓	The variant has been reported to segregate in at least five informative meioses (PMID 25212744, internal database). Review of UBE3A variants identified in a cohort of 2515 AS patients. Variant was identified identified in one proband, found to be maternally inherited, and was present in proband's affected sister and in two affected maternal cousins. PubMed:25212744
PM2_Supporting	✓	The p.Thr106Lys variant in UBE3A is absent from gnomAD
PS3_Supporting	✓	Protein expression analysis in transfected cell lines has shown that this variant reduces protein function (PMID 26255772)

Protein expression analysis in transfected cell lines found that protein levels were significantly lower than wild type UBE3A, suggesting that this variant promotes hyperactive self-degradation of UBE3A, a novel gain-of-function mechanism that reduces UBE3A level (see Figure S1B-E, Table S1). PubMed:26255772

Curation History

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