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Variant: NM_130839.5(UBE3A):c.1576C>T (p.Arg526Cys)

Version: 2.0

CA16619907

418572 (ClinVar)

Gene: UBE3A (HGNC:7337)
Condition: Angelman syndrome (MONDO:0007113)
Inheritance Mode: Autosomal dominant inheritance
UUID: ee548715-7a99-499a-aff8-b87446f02a4c
Approved on: 2025/2/28
Published on: 2025/3/7

HGVS expressions

NM_130839.5:c.1576C>T
NM_130839.5(UBE3A):c.1576C>T (p.Arg526Cys)
NC_000015.10:g.25370598G>A
CM000677.2:g.25370598G>A
NC_000015.9:g.25615745G>A
CM000677.1:g.25615745G>A
NC_000015.8:g.23166838G>A
NG_009268.1:g.73384C>T
ENST00000438097.6:c.1516C>T
ENST00000625778.3:c.1516C>T
ENST00000635914.1:c.1516C>T
ENST00000637886.1:c.1576C>T
ENST00000638011.1:c.1516C>T
ENST00000638155.1:c.1516C>T
ENST00000648336.2:c.1576C>T
ENST00000649550.1:c.1516C>T
ENST00000650110.1:c.1585C>T
ENST00000675000.1:n.2251C>T
ENST00000675177.1:c.1399C>T
ENST00000675593.1:n.4272C>T
ENST00000232165.7:c.1516C>T
ENST00000397954.6:c.1585C>T
ENST00000428984.6:c.1516C>T
ENST00000438097.5:c.1516C>T
ENST00000566215.5:c.1516C>T
ENST00000614096.4:c.1576C>T
ENST00000625778.2:c.1516C>T
ENST00000630424.2:c.1516C>T
NM_000462.3:c.1585C>T
NM_130838.1:c.1516C>T
NM_130839.2:c.1576C>T
NM_000462.5:c.1585C>T
NM_001354505.1:c.1576C>T
NM_001354506.1:c.1516C>T
NM_001354507.1:c.1516C>T
NM_001354508.1:c.1516C>T
NM_001354509.1:c.1516C>T

NM_001354511.1:c.1516C>T
NM_001354512.1:c.1516C>T
NM_001354513.1:c.1516C>T
NM_001354523.1:c.1516C>T
NM_001354526.1:c.1516C>T
NM_001354538.1:c.1576C>T
NM_001354539.1:c.1516C>T
NM_001354540.1:c.1516C>T
NM_001354541.1:c.1516C>T
NM_001354542.1:c.1516C>T
NM_001354543.1:c.1516C>T
NM_001354544.1:c.1516C>T
NM_001354545.1:c.1576C>T
NM_001354546.1:c.1399C>T
NM_001354547.1:c.1516C>T
NM_001354548.1:c.1516C>T
NM_001354549.1:c.1516C>T
NM_001354550.1:c.361+4867C>T
NM_001354551.1:c.301+4867C>T
NM_130838.3:c.1516C>T
NM_130839.4:c.1576C>T
NR_146177.1:n.18393-20998G>A
NR_148916.1:n.2124C>T
NM_001354506.2:c.1516C>T
NM_001354507.2:c.1516C>T
NM_001354508.2:c.1516C>T
NM_001354509.2:c.1516C>T
NM_001354511.2:c.1516C>T
NM_001354512.2:c.1516C>T
NM_001354513.2:c.1516C>T
NM_001354523.2:c.1516C>T
NM_001354538.2:c.1576C>T
NM_001354539.2:c.1516C>T
NM_001354540.2:c.1516C>T
NM_001354541.2:c.1516C>T
NM_001354542.2:c.1516C>T
NM_001354543.2:c.1516C>T
NM_001354544.2:c.1516C>T
NM_001354545.2:c.1576C>T
NM_001354546.2:c.1399C>T
NM_001354547.2:c.1516C>T
NM_001354548.2:c.1516C>T
NM_001354549.2:c.1516C>T
NM_001354550.2:c.361+4867C>T
NM_001354551.2:c.301+4867C>T
NM_001374461.1:c.1516C>T
NM_130838.4:c.1516C>T
NR_148916.2:n.2092C>T

Met criteria codes 7

Expert Panel

Pathogenic

PM6 PS3_Supporting PS4 PM2_Supporting PP1 PP3 PP4

Evidence Links 0

Rett and Angelman-like Disorders VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Rett and Angelman-like Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for UBE3A Version 5.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The c.1576C>T (p.Arg526Cys) variant in the UBE3A gene has been observed in at least 5 individuals with Angelman syndrome (PMID: 10647895, 19213023, 23708187, 25212744; GeneDx: internal database) (PS4). The p.Arg526Cys variant in UBE3A has been reported as an unconfirmed de novo occurrence in a individual with Angelman syndrome (PMID: 10647895) (PM6). The variant has been reported to segregate in two informative meioses (PMID: 23708187) (PP1). The computational predictor REVEL gives a score of 0.866, which is above the threshold of 0.644, evidence that correlates with impact to UBE3A function (PP3). The p.Arg526Cys variant in UBE3A has been reported in an individual with a clinical phenotype suggestive of Angelman syndrome (PMID: 10647895) (PP4). The p.Arg526Cys variant in UBE3A is absent from gnomAD v4.1 (PM2_Supporting). Protein expression analysis in transfected cell lines has shown that this variant destabilizes the protein, demonstrated by significantly reduced protein levels (PMID: 26255772) (PS3_Supporting). In summary, the p.Arg526Cys variant in UBE3A is classified as Pathogenic for Angelman syndrome based on the ACMG/AMP criteria (PS4, PM6, PP1, PP3, PP4, PM2_supporting, PS3_supporting) (UBE3A specifications version 5.0; curation approved on 2/28/2025).

Met criteria codes

PM6 ✔	The p.Arg526Cys variant in UBE3A has been reported as an unconfirmed de novo occurrence in a individual with Angelman syndrome (PMID: 10647895).
PS3_Supporting ✔	Protein expression analysis in transfected cell lines has shown that this variant destabilises the protein, demonstrated by significantly reduced protein levels (PMID: 26255772)
PS4 ✔	The p.Arg526Cys variant in the UBE3A gene has been observed in at least 5 other individuals with Angelman syndrome (PMID: 10647895, 19213023, 23708187, 25212744; GeneDx: internal database). (PS4)
PM2_Supporting ✔	The p.Arg506Cys variant in UBE3A is absent from gnomAD v4.1 (PM2_Supporting).
PP1 ✔	The variant has been reported to segregate in two informative meioses (PMID 23708187) (PP1).
PP3 ✔	The computational predictor REVEL gives a score of 0.866, which is above the threshold of 0.644, evidence that correlates with impact to UBE3A function (PP3).
PP4 ✔	The p.Arg526Cys variant in UBE3A has been reported in an individual with a clinical phenotype suggestive of Angelman syndrome (PMID 10647895) (PP4).

Curation History

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