

Variant: *NM_000531.6(OTC):c.498G>T (p.Leu166Phe)*

Version: 1.0

CA10385879 [↗](#)

1167469 (ClinVar) [↗](#)

Gene: OTC ([HGNC:5009](#))

Condition: ornithine carbamoyltransferase deficiency ([MONDO:0010703](#))

Inheritance Mode: X-linked inheritance (recessive (HP:0001419))

UUID: 153ca2bf-d5f1-4655-af30-15dffe98098a

Approved on: 2026/5/20

Published on: 2026/5/30

HGVS expressions

NM_000531.6:c.498G>T

NM_000531.6(OTC):c.498G>T (p.Leu166Phe)

NC_000023.11:g.38401386G>T

CM000685.2:g.38401386G>T

NC_000023.10:g.38260639G>T

CM000685.1:g.38260639G>T

NC_000023.9:g.38145583G>T

NG_008471.1:g.53904G>T

ENST00000039007.5:c.498G>T

ENST000000643344.1:c.*248G>T

ENST00000039007.4:c.498G>T

ENST00000465127.1:c.172-264735G>T

ENST00000488812.1:n.535G>T

NM_000531.5:c.498G>T

Benign

Met criteria codes **2**

BA1

BS3_Supporting

Not Met criteria codes **8**

BP4

BS1

PP3

PP4

PM1

PM5

PM2

PS3

Evidence Links **1**

Expert Panel

[Urea Cycle Disorders VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** *ClinGen Urea Cycle Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for OTC Version 1.0.0*

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Urea Cycle Disorders VCEP

The NM_000531.6:c.498G>T variant in OTC is a missense variant predicted to cause substitution of leucine by phenylalanine at amino acid 166 (p.Leu166Phe). To our knowledge, this variant has not been reported in the literature in any individuals with OTC deficiency. The Grpmax Filtering allele frequency in gnomAD v4.1.0 is 0.0001094 (5/45704 alleles) in the Admixed American population, with 21 hemizygotes/homozygotes across all populations which is higher than the ClinGen UCD VCEP threshold (>10 hemizygotes/homozygotes) for

BA1, and therefore meets this criterion (**BA1**). Expression of the variant in yeast resulted in **71.5%** which is between **65** and **80%** indicating supporting evidence for no impact on OTC function (**PMID: 37146589**) (**BS3_Supporting**). The computational predictor **REVEL** gives a score of **0.57** which is between **0.644** and **0.290** and indicates an uncertain impact on OTC function. In summary, this variant meets the criteria to be classified as benign for OTC deficiency based on the **ACMG/AMP** criteria applied, as specified by the **ClinGen Urea Cycle Disorders Variant Curation Expert Panel (OTC specifications version 1.0.0): BA1, BS3_Supporting**.

Met criteria codes

BA1			The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001094 (5/45704 alleles) in the Admixed American population and there are 21 hemizygotes in total.
BS3_Supporting			Growth assay in yeast showed >65% and <80% of wild-type OTC growth activity, indicating that this variant does not impact protein function (PMID: 37146589, BS3_Supporting).
			PMID: 37146589: variant shown to result in 71.5% of wild-type growth in yeast assay PubMed:37146589 

Not Met criteria codes

BP4			The computational predictor REVEL gives a score of 0.57 which is between 0.644 and 0.290, evidence that indicates an uncertain impact on OTC function.
BS1			The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001094 (5/45704 alleles) in the Admixed American population and there are 21 hemizygotes in total.
PP3			The computational predictor REVEL gives a score of 0.57, which is between 0.644 and 0.290, evidence that indicates an uncertain impact on OTC function.
PP4			No affected individuals with this variant have been reported
PM1			Not in any of the designated critical residues per the UCD VCEP specifications
PM5			p.L166S is VUS in ClinVar (ID: 3069921)
PM2			The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001094 (5/45704 alleles) in the Admixed American population and there are 21 hemizygotes in total.
PS3			PMID: 37146589: variant shown to result in 71.5% (hypomorphic range) of wild-type growth in yeast assay

Curation History 

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.