

Variant: *NM_000531.6(OTC):c.1025T>C (p.Leu342Pro)*

Version: 1.1

CA412728043 [↗](#)

943237 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 9018a567-e5e9-47ce-aa35-592590b6e29d

Approved on: 2026/6/11

Published on: 2026/9/11

HGVS expressions

NM_000531.6:c.1025T>C

NM_000531.6(OTC):c.1025T>C (p.Leu342Pro)

NC_000023.11:g.38421042T>C

CM000685.2:g.38421042T>C

NC_000023.10:g.38280295T>C

CM000685.1:g.38280295T>C

NC_000023.9:g.38165239T>C

NG_008471.1:g.73560T>C

ENST00000039007.5:c.1025T>C

ENST000000643344.1:c.*775T>C

ENST00000039007.4:c.1025T>C

ENST000000465127.1:c.172-245079T>C

NM_000531.5:c.1025T>C

Likely Pathogenic

Met criteria codes **3**

PP3_Strong

PM2_Supporting

PS3_Moderate

Not Met criteria codes **9**

BS1

BP4

BP1

PS1

BA1

PP2

PP4

PM1

PM5

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

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

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

Evidence submitted by expert panel

Urea Cycle Disorders VCEP

The NM_000531.6:c.1025T>C variant in OTC is a missense variant predicted to cause substitution of leucine by proline at amino acid 342 (p.Leu342Pro). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a SCORE of 0.958, which is above the threshold of ≥ 0.932 to apply PP3_Strong, evidence that correlates with impact to OTC function (PP3_Strong).

Quantitative growth assay in yeast strains showed <5% wild-type growth activity, indicating that this variant impacts protein function (PMID: 37146589) (PS3_Moderate). In summary, this variant meets the criteria to be classified as Likely Pathogenic for X-linked ornithine

carbamoyltransferase deficiency. ACMG/AMP criteria met, as specified by the ClinGen Urea Cycle Disorders VCEP (OTC specifications version 1.0.0): PM2_Supporting, PP3_Strong, PS3_Moderate.			
Met criteria codes			
PP3_Strong			The REVEL computational prediction analysis tool produced a score of 0.958, which is above the threshold necessary to apply PP3_Strong (≥ 0.932).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting)
PS3_Moderate			Quantitative growth assay in yeast strains showed <5% wild-type growth activity, indicating that this variant impacts protein function (PMID: 37146589) (PS3_Moderate).
			PMID: 37146589: shown to result in <5% wild-type OTC growth activity in yeast assay, consistent with impairing protein function PubMed:37146589 

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No same AA change found
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			Patient described by Bernal et al. could possibly have this variant, but there are typos in the article. The variant is named as c.1025T>G (p.Leu342Pro) in Table 2, but c.1025T>G (p.Lys342Pro) in Supplementary Material. It is rather unclear if this is the same variant that is being curated. Maybe contact paper's authors?
PM1			This variant does not reside within a region of OTC that is defined as a mutational hotspot or critical functional domain by the ClinGen Urea Cycle Disorders VCEP.
PM5			No other MS vrts were found

Curation History [↗](#)



Showing 1 to 2 of 2 rows

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