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_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
ENST00000643344.1:c.*775T>C
ENST00000039007.4:c.1025T>C
ENST00000465127.1:c.172-245079T>C
NM_000531.5:c.1025T>C

Likely Pathogenic

Met criteria codes 3

PS3_Moderate PP3_Strong PM2_Supporting

Not Met criteria codes 9

PP2 PP4 PM1 PM5 BA1 BS1 PS1 BP4 BP1

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

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**
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)

Not Met criteria codes

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
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No same AA change found
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

Curation History

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