

Variant: *NM_000531.6(OTC):c.264A>T (p.Lys88Asn)*

Version: 2.0

CA224521 [↗](#)

97145 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 1d0181ec-e87f-422c-b403-c9627824cc17

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HGVS expressions

NM_000531.6(OTC):c.264A>T (p.Lys88Asn)

NM_000531.6:c.264A>T

NC_000023.11:g.38369843A>T

CM000685.2:g.38369843A>T

NC_000023.10:g.38229096A>T

CM000685.1:g.38229096A>T

NC_000023.9:g.38114040A>T

NG_008471.1:g.22361A>T

ENST00000039007.5:c.264A>T

ENST000000643344.1:c.264A>T

ENST00000039007.4:c.264A>T

ENST000000465127.1:c.172-296278A>T

ENST000000488812.1:n.353+3A>T

NM_000531.5:c.264A>T

Likely Pathogenic

Met criteria codes 5

PS4_Moderate

PP4_Moderate

PP3_Moderate

BS3_Supporting

PM2_Supporting

Not Met criteria codes 6

PS3

PP2

BA1

BS1

BP4

BP1

Evidence Links 0

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.264A>T variant in OTC is a missense variant predicted to cause substitution of lysine by asparagine at amino acid 88 (p.Lys88Asn). One male patient with this variant developed hyperammonemic coma with 8 months of age. OTC enzymatic activity in liver tissue was reduced (3% wildtype) which is highly specific for OTC deficiency (PP4_Moderate, PMID 8260194). This variant has been reported in 2 additional probands with biochemical and clinical evidence of OTC deficiency (PS4_Moderate; PMID: 8956038, 25573644).

Another patient with this variant have been reported in the literature, but clinical and biochemical features were not reported (PMID: 25433810). The highest population minor allele frequency in gnomAD v4.1 (Grpmax FAF was not available for this variant) is 0.000001127 (1/887338 alleles) in European (non-Finnish) population, with 1 hemizygotes across all populations. This is lower than the ClinGen UCD VCEP threshold (<0.000015 AND $\leq$ 1 hemizygotes) for PM2_Supporting, meeting this criterion (PM2_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). The computational predictor REVEL gives a score of 0.88, which is between 0.773 and 0.932, evidence that correlates with moderate impact to OTC function (PP3_Moderate), additionally SpliceAI delta score is 0.24 for a loss of the canonical acceptor, and 0.18 for loss of the canonical donor of this exon. In summary, this variant meets the criteria to be classified as Likely Pathogenic for X-linked ornithine carbamoyltransferase deficiency. Although there are both pathogenic and benign types of evidence for this variant, the pathogenic/benign evidence is not considered inconsistent with the final classification. ACMG/AMP criteria applied, as specified by the ClinGen Urea Cycle Disorders VCEP (OTC specifications version 1.0.0), 02/08/2025: PP4_Moderate (+2), PS4_Moderate (+2), PP3_Moderate (+2), PM2_Supporting (+1), BS3_Supporting (-1).

Met criteria codes

PS4_Moderate			This variant has been reported in 2 additional probands with biochemical and clinical evidence of OTC deficiency (PS4_Moderate; PMID: 8956038, 25573644). Another patient with this variant have been reported in the literature, but clinical and biochemical features were not reported (PMID: 25433810).
PP4_Moderate			One male patient with this variant developed hyperammonemic coma with 8 months of age. OTC enzymatic activity in liver tissue was reduced (3% wildtype) which is highly specific for OTC deficiency (PP4_Moderate, PMID 8260194).
PP3_Moderate			The computational predictor REVEL gives a score of 0.88, which is between 0.773 and 0.932, evidence that correlates with moderate impact to OTC function (PP3_Moderate).
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).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1 (Grpmax FAF was not available for this variant) is 0.000001127 (1/887338 alleles) in European (non-Finnish) population, with 1 hemizygotes across all populations. This is lower than the ClinGen UCD VCEP threshold (<0.000015 AND $\leq$ 1 hemizygotes) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PS3			
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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

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 		
Showing 1 to 2 of 2 rows		

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