

Variant: *NM_000531.6(OTC):c.241T>C (p.Ser81Pro)*

Version: 1.1

CA412716867 [↗](#)

1504390 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 0b1c7ad9-4053-46e0-aaff-aeef80d2e106

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HGVS expressions

NM_000531.6(OTC):c.241T>C (p.Ser81Pro)

NM_000531.6:c.241T>C

NC_000023.11:g.38369820T>C

CM000685.2:g.38369820T>C

NC_000023.10:g.38229073T>C

CM000685.1:g.38229073T>C

NC_000023.9:g.38114017T>C

NG_008471.1:g.22338T>C

ENST00000039007.5:c.241T>C

ENST000000643344.1:c.241T>C

ENST00000039007.4:c.241T>C

ENST000000465127.1:c.172-296301T>C

ENST000000488812.1:n.333T>C

NM_000531.5:c.241T>C

Likely Pathogenic

Met criteria codes 4

PP3_Moderate

PM2_Supporting

PS2

PP4

Not Met criteria codes 1

PM1

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(OTC):c.241T>C variant in OTC is a missense variant predicted to cause substitution of serine by proline at amino acid 81 (p.Ser81Pro). This variant has been reported as a de novo variant (confirmed by parental testing) in one (hemizygous) male individual with biochemical evidence of OTC deficiency (elevated ammonia, normal citrulline, and elevated urine uracil) (PS2, PP4) (PMID: 38802913). It has also been reported in 1 heterozygous female with elevated ammonia without further biochemical testing reported (PMID: 32447331),

such that this individual cannot be counted for PP4 and/or PS4 as per UCD VCEP specifications. This variant is absent in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.854, which is between 0.773 and 0.932, and Moderate evidence of impact on OTC/NAGS/CPS1 function (PP3_Moderate). In summary, this variant meets the criteria to be classified as likely pathogenic 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): PS2, PM2_Supporting, PP3, PP4.

Met criteria codes

PP3_Moderate			The REVEL score is 0.854, which is between ≥ 0.773 and < 0.932 , meeting UCD VCEP cutoff for use of PP3_Moderate.
PM2_Supporting			Absent from gnomAD v4.1.0
PS2			Identified in 1 hemizygous male with elevated ammonia and normal citrulline, confirmed de novo via parental testing (PMID: 38802913)
PP4			Identified in 1 hemizygous male with elevated ammonia and normal citrulline (0.5 pts for PP4), confirmed de novo via parental testing (PMID: 38802913). Patient also had elevated urine uracil, but urine orotic acid level was not noted.

Not Met criteria codes

PM1			Not in any of the designated critical residues by the UCD VCEP
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Curation History



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