

Variant: *NM_000531.6(OTC):c.903A>T (p.Leu301Phe)*

Version: 1.0

CA224823 [↗](#)

97350 (ClinVar) [↗](#)

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

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

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

UUID: 441513fd-0c35-4db6-911d-bb1ec0e4d4dd

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HGVS expressions

NM_000531.6:c.903A>T

NM_000531.6(OTC):c.903A>T (p.Leu301Phe)

NC_000023.11:g.38411897A>T

CM000685.2:g.38411897A>T

NC_000023.10:g.38271150A>T

CM000685.1:g.38271150A>T

NC_000023.9:g.38156094A>T

NG_008471.1:g.64415A>T

ENST00000039007.5:c.903A>T

ENST00000643344.1:c.*653A>T

ENST00000039007.4:c.903A>T

ENST00000465127.1:c.172-254224A>T

NM_000531.5:c.903A>T

Likely Pathogenic

Met criteria codes **5**

PS3_Moderate

PP3_Moderate

PS4_Moderate

PM2_Supporting

PP4_Moderate

Not Met criteria codes **2**

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 1.0.0*

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

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

Evidence submitted by expert panel

Urea Cycle Disorders VCEP

The NM_000531.6:c.903A>T (p.Leu301Phe) variant in OTC affects a base pair that is highly conserved in vertebrates and is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a SCORE of 0.86, which is between 0.773 and 0.932, evidence that correlates with Moderate impact to OTC function (PP3_Moderate). A male patient with this variant has been reported in the literature with hyperammonemia, low citrulline, elevated urine orotic acid, and enzyme activity 3% in patient cells (PP4_Moderate; PMID:8008687, 11793483); the patient had late onset disease. This variant has been reported in two additional male probands observed with late onset

OTC deficiency and hyperammonemia. (PS4_Moderate; PMID: 22340867, 35949797). Growth assay in yeast showed 0.029of wild-type OTC growth activity, indicating that this variant impacts protein function (PMID: 37146589, <50% - PS3_Moderate). In summary, this variant meets criteria to be classified as a Likely Pathogenic variant for OTC. OTC-specific ACMG/AMP criteria applied (OTC specifications version 1.0.0): PS4_Moderate, PS3_Moderate, PM2_Supporting, PP3_Moderate, PP4_Moderate.

Met criteria codes

PS3_Moderate			Growth assay in yeast showed <50% of wild-type OTC growth activity, indicating that this variant impacts protein function (PMID: 37146589, PS3_Moderate).
The growth rate of yeast cells expressing the L301F human OTC variant was 1.7% of the growth rate of yeast cells expressing wild-type OTC. PubMed:37146589 			
PP3_Moderate			The computational predictor REVEL gives a SCORE of 0.86, which is between 0.773 and 0.932, evidence that correlates with Moderate impact to OTC function (PP3_Moderate).
PS4_Moderate			This variant has been reported in two additional male probands observed with late onset OTC deficiency and hyperammonemia. (PS4_Moderate; PMID: 22340867, 35949797).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting)
PP4_Moderate			A male patient with this variant displayed hyperammonemia, high urinary orotate and undetectable citrulline; patient derived cells had 3% of normal OTC enzyme activity. This is highly specific for late onset OTC deficiency (PP4_Moderate, PMID: 11793483, 2 points).

Not Met criteria codes

PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			The current variant is the only variant found in this codon in ClinVar.

Curation History

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