

Variant: *NM_000531.6(OTC):c.275G>A (p.Arg92Gln)*

Version: 1.0

CA285805 [↗](#)

97152 (ClinVar) [↗](#)

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

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

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

UUID: 1ae44276-7b0e-4b46-af1a-9b1a2ce7e765

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HGVS expressions

NM_000531.6:c.275G>A

NM_000531.6(OTC):c.275G>A (p.Arg92Gln)

NC_000023.11:g.38369854G>A

CM000685.2:g.38369854G>A

NC_000023.10:g.38229107G>A

CM000685.1:g.38229107G>A

NC_000023.9:g.38114051G>A

NG_008471.1:g.22372G>A

ENST00000039007.5:c.275G>A

ENST000000643344.1:c.275G>A

ENST00000039007.4:c.275G>A

ENST000000465127.1:c.172-296267G>A

ENST000000488812.1:n.353+14G>A

NM_000531.5:c.275G>A

Pathogenic

Met criteria codes **6**

PS4 PP4_Moderate PS3_Moderate

PM1 PP3_Strong PM2_Supporting

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 1.0.0

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

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

Evidence submitted by expert panel

Urea Cycle Disorders VCEP

The NM_000531.6:c.275G>A (p.Arg92Gln) variant in OTC is a missense variant in biologically relevant exon 3. Computational evidence strongly suggests that this variant affects protein function (PP3_Strong). This variant is absent in gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in the literature in 7 patients; 3 described as having OTC deficiency, but no details were provided regarding plasma amino acids/ammonia, urine orotic acid, or enzyme activity in patient cells; 1 patient was a male with neonatal onset disease

(PMID: 1671317); disease onset and sex information were not provided for 2 patients (PMID: 19138872). Clinical and biochemical symptoms were described for the remaining 4 patients (PMID: 26753873, 10799432, 36303552, 34670952) (PS4). Biochemical symptoms, specific to OTC deficiency, were reported in the literature for 2 patients (PMID: 30285816, 33272297; PP4_Moderate). This variant is located in a critical and well-established functional domain (the carbamylphosphate binding site at Arg-92) [PMID:9852088, 10813810, 11237854] (PM1). Additionally, this variant has been shown to result in <5% wild-type OTC growth activity in yeast assay, suggesting that this variant may impact protein function (PMID: 37146589, PS3_Supporting). In summary, this variant meets the criteria to be classified as a pathogenic variant 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): PP3_Strong, PM2_Supporting, PS4, PP4_Moderate, PM1, PS3_Supporting

Met criteria codes

PS4			7 patients with biochemical symptoms of OTC deficiency.
PP4_Moderate			2 patients with clinical and biochemical symptoms of OTC deficiency
PS3_Moderate			PMID: 37146589: shown to result in <5% wild-type OTC growth activity in yeast assay, suggesting that this variant may impact protein function
PM1			This variant is located in a critical and well-established functional domain (the carbamylphosphate binding site at Arg-92) [PMID:9852088, 10813810, 11237854].
PP3_Strong			The REVEL score is 0.976, which is above the 0.932 threshold. According to the OTC Gene Specifications, the strength of evidence can be changed from Supporting to Strong.
PM2_Supporting			The variant is absent from gnomAD v4.1.0, ESP, and 1000G project.

Curation History

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