

Variant: *NM_000531.6(OTC):c.119G>A (p.Arg40His)*

Version: 1.2

CA224454 [↗](#)

11014 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 556b917f-15e3-4709-81a6-12df78d7d07e

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HGVS expressions

NM_000531.6:c.119G>A

NM_000531.6(OTC):c.119G>A (p.Arg40His)

NC_000023.11:g.38367332G>A

CM000685.2:g.38367332G>A

NC_000023.10:g.38226585G>A

CM000685.1:g.38226585G>A

NC_000023.9:g.38111529G>A

NG_008471.1:g.19850G>A

ENST00000039007.5:c.119G>A

ENST000000643344.1:c.119G>A

ENST00000039007.4:c.119G>A

ENST000000465127.1:c.172-298789G>A

ENST000000488812.1:n.211G>A

NM_000531.5:c.119G>A

Pathogenic

Met criteria codes **5**

PP4_Moderate

PP1_Strong

PS4

PM2_Supporting

PS3_Moderate

Not Met criteria codes **8**

BA1

BS1

BP4

BP1

PS1

PP2

PP3

PM1

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 c.119G>A variant in OTC is a missense variant predicted to cause substitution of arginine by histidine at amino acid 40 (p.Arg40His). One patient with this variant displayed hyperammonemia, elevated glutamine, normal citrulline, with elevated urine orotic acid, which is highly specific for ornithine transcarbamylase deficiency (PMID:25026867; PP4_Moderate). This variant has been reported in 13 additional male and 1 female probands with biochemical or clinical evidence of OTC deficiency (PMID:6635166, 9286441, 23209112, 17334707,

7860066, 19893582, 25026867, 21070677, 11260212, 9048915; PS4_VeryStrong). This variant is absent from gnomAD v4.1 (PM2_Supporting). Growth assay in yeast showed <50% of wild-type OTC growth activity, indicating that this variant have a impact protein function (PMID: 37146589; PS3_Supporting). Multiple affected family members (≥5 informative segregations, PP1 strong; PMID:16635166, 9286441, 11260212, 9048915). Another missense variant c.118C>T (p.Arg40Cys) is Pathogenic/Likely Pathogenic, and c.119G>T (p.Arg40Leu) is Likely Pathogenic in ClinVar, however PM5 criteria is not being utilized in this curation. The computational predictor REVEL gives a SCORE of 0.613, which is below the threshold of 0.644, evidence that correlates with uncertain impact to OTC function. In summary, this variant meets the criteria to be classified as Pathogenic for X-linked ornithine carbamoyltransferase deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Urea Cycle Disorders VCEP: PP4_Moderate (+2), PS4_VeryStrong (+8), PM2_Supporting (+1), PS3_Supporting (+1), PP1_Strong (+4)

Met criteria codes

PP4_Moderate			One patient with this variant displayed hyperammonemia (0.25), elevated glutamine and normal citrulline (0.5), with elevated urine orotic acid (1), which is highly specific for ornithine transcarbamylase deficiency, with evidence total ≥1.5 points (PP4_Moderate, PMID: 25026867).
PP1_Strong			Multiple affected family members (≥5 informative segregations)
PS4			13 additional male & 1 female probands observed (PMID: 21070677, PMID: 11260212, PMID: 7860066, PMID: 17334707, PMID: 16635166, PMID: 23209112) PS4_VeryStrong
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting)
PS3_Moderate			Growth assay in yeast showed <50% of wild-type OTC growth activity, indicating that this variant have a impact protein function (PMID: 37146589, PS3_Supporting).
			Growth assay in yeast showed <50% of wild-type OTC growth activity, indicating that this variant have a impact protein function (PMID: 37146589, PS3_Supporting). PubMed:37146589 

Not Met criteria codes

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			The computational predictor REVEL gives a SCORE of 0.613, which is above the threshold of 0.644, evidence that correlates with uncertain impact to OTC function.
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3		✖	The computational predictor REVEL gives a SCORE of 0.613, which is below the threshold of 0.644, evidence that correlates with uncertain impact to OTC function.
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
		  
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