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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
Approved on: Tue, 15 Sep 2026 00:00:00 +0000
Published on: Tue, 15 Sep 2026 00:00:00 +0000

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
ENST00000643344.1:c.119G>A
ENST00000039007.4:c.119G>A
ENST00000465127.1:c.172-298789G>A
ENST00000488812.1:n.211G>A
NM_000531.5:c.119G>A

Pathogenic

Met criteria codes 5

PM2_Supporting PS3_Moderate PP4_Moderate PS4 PP1_Strong

Not Met criteria codes 8

BA1 PP2 PP3 PM1 BS1 PS1 BP4 BP1

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

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
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).
PS4	✔	13 additional male & 1 female probands observed (PMID: 21070677, PMID: 11260212, PMID: 7860066, PMID: 17334707, PMID: 16635166, PMID: 23209112) PS4_VeryStrong
PP1_Strong	✔	Multiple affected family members (≥5 informative segregations)

Not Met criteria codes

BA1	✖	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
BS1	✖	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
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

Curation History

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