

Variant: *NM_000531.6(OTC):c.118C>T (p.Arg40Cys)*

Version: 2.0

CA090910 [↗](#)

11013 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

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HGVS expressions

NM_000531.6(OTC):c.118C>T (p.Arg40Cys)

NM_000531.6:c.118C>T

NC_000023.11:g.38367331C>T

CM000685.2:g.38367331C>T

NC_000023.10:g.38226584C>T

CM000685.1:g.38226584C>T

NC_000023.9:g.38111528C>T

NG_008471.1:g.19849C>T

ENST00000039007.5:c.118C>T

ENST000000643344.1:c.118C>T

ENST00000039007.4:c.118C>T

ENST000000465127.1:c.172-298790C>T

ENST000000488812.1:n.210C>T

NM_000531.5:c.118C>T

Likely Pathogenic

Met criteria codes **6**

PS3_Moderate

PP1

PM5

PP3_Moderate

PS4_Supporting

PP4_Moderate

Not Met criteria codes **2**

PM2

BS1

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.118C>T variant in OTC is a missense variant predicted to cause substitution of Arg by Cys at amino acid 40 (p.Arg40Cys). Predictor REVEL gives a score of 0.902, which is between 0.773 and 0.932, and Moderate evidence of impact on OTC function (PP3_Moderate). The p.Arg40Cys also has one patient with this variant displaying hyperammonemia, urinary orotate, 3% OTC activity, which is highly specific for OTC deficiency (PMID: 7860066; PP4_Moderate). Another missense variant [c.119G>A, p.Arg40His; ClinVar

Variation ID 11014], in the same codon, has been classified as pathogenic for OTC deficiency by the ClinGen Urea Cycle Disorders VCEP (PM5). The growth assay in yeast showed 31.1±0.07% of wild-type OTC growth activity, indicating that this variant impacts protein function (PMID: 37146589, PS3_Moderate). The Grpmax Filtered allele frequency in gnomAD v4.1.0 is 0.00000917, which is lower than the ClinGen UCD VCEP’s threshold for PM2_Supporting (<0.000015), however, there are 6 hemizygotes across all populations. While the presence of 6 hemizygotes meets BS2 criterion as specified by the UCD VCEP, this variant is excluded from BS2 given its known late onset phenotype. This variant has been reported in 1 additional proband with hyperammonemia and orotic aciduria (PMID: 20406775; PS4_supporting). The variant has been reported to segregate with OTC in the mother and sister affected PP1_SUPPORTING; PMID:7860066 In summary, this variant meets the criteria for being classified as likely pathogenic for OTC deficiency. ACMG/AMP criteria applied, as specified by the ClinGen UCD VCEP (OTC specifications version 1.0.0): PP3_moderate (+2), PP4_Moderate (+2), PM5 (+2), PS3_Moderate (+2), and PS4_Supporting (+1).

Met criteria codes			
PS3_Moderate			Growth assay in yeast showed <31.1% of wild-type OTC growth activity, indicating that this variant impacts protein function (PMID: 37146589, PS3_Moderate).
PP1			The variant has been reported to segregate with OTC in the mother and sister affected PP1_SUPPORTING; PMID:7860066
PM5			Another missense variant [c.119G>A, p.Arg40His] [ClinVar Variation ID 11014, in the same codon has been classified as pathogenic for OTC deficiency by the ClinGen Urea Cycle Disorders VCEP (PM5).
PP3_Moderate			The computational predictor REVEL gives a score of 0.902, which is between 0.773 and 0.932, and Moderate evidence of impact on OTC function (PP3_Moderate).
PS4_Supporting			This variant has been reported in 1 additional proband with hyperammonemia and orotic aciduria PS4_supporting; PMID: 20406775
PP4_Moderate			One patient with this variant displayed hyperammonemia, urinary orotate, 3% OTC activity which is highly specific for OTC deficiency PP4_Moderate

Not Met criteria codes			
PM2			The Grpmax Filtered allele frequency in gnomAD v4.1.0 is 0.00000917, which is lower than the ClinGen UCD VCEP’s threshold for PM2_Supporting (<0.000015), but there are 6 hemizygotes across all populations, which is greater than ≤1 hemizygote required to apply PM2 evidence
BS1			The Grpmax Filtered allele frequency in gnomAD v4.1.0 is 0.00000917, which is lower than the ClinGen UCD VCEP’s threshold for BS1 (>0.002000 (0.2%)).

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