

Variant: *NM_000531.6(OTC):c.617T>G (p.Met206Arg)*

Version: 1.1

CA224711 [↗](#)

11012 (ClinVar) [↗](#)

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

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

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

UUID: 9ace43c2-b0d5-4cfa-ac9a-b572b6d58dec

Approved on: 2026/5/20

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HGVS expressions

NM_000531.6(OTC):c.617T>G (p.Met206Arg)

NM_000531.6:c.617T>G

NC_000023.11:g.38403694T>G

CM000685.2:g.38403694T>G

NC_000023.10:g.38262947T>G

CM000685.1:g.38262947T>G

NC_000023.9:g.38147891T>G

NG_008471.1:g.56212T>G

ENST00000039007.5:c.617T>G

ENST000000643344.1:c.*367T>G

ENST00000039007.4:c.617T>G

ENST000000465127.1:c.172-262427T>G

NM_000531.5:c.617T>G

Pathogenic

Met criteria codes **6**

PP4_Moderate

PS3_Moderate

PP3_Moderate

PM6

PS4_Supporting

PM2_Supporting

Not Met criteria codes **7**

BP4

BP1

BS1

BS3

PP2

BA1

PS2

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.617T>G variant in OTC is a missense variant predicted to cause substitution of methionine by arginine at amino acid 206 (p.Met206Arg). One male patient with this variant displayed in the first few days of life hyperammonemia, high glutamine, high orotic acid, and reduced liver OTC activity, which is highly specific for OTC deficiency (PP4_Moderate, PMID: 10405441). The variant was not detected in the unaffected mother of this patient by targeted testing (PM6). This variant has been reported in 1 additional proband with biochemical and clinical evidence of OTC deficiency (PS4_Supporting; PMID: 25994866). 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 impacts protein function (PMID: 37146589, PS3_Moderate). The computational predictor REVEL gives a score of 0.875, which is between 0.773 and 0.932, evidence that correlates with moderate impact to OTC function (PP3_Moderate). 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 (OTC specifications version 1.0.0), 02/10/2025: PP4_Moderate, PM6, PS4_Supporting, PM2_Supporting, PS3_Moderate, PP3_Moderate.

Met criteria codes

PP4_Moderate			One male patient with this variant displayed in the first few days of life hyperammonemia, high glutamine, high orotic acid, and reduced liver OTC activity, which is highly specific for OTC deficiency (PP4_Moderate, PMID: 10405441). The variant was not detected in the unaffected mother of this patient (PM6).
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).
PP3_Moderate			The computational predictor REVEL gives a score of 0.875, which is between 0.773 and 0.932, evidence that correlates with moderate impact to OTC function (PP3_Moderate).
PM6			One male patient with this variant displayed in the first few days of life hyperammonemia, high glutamine, high orotic acid, and reduced liver OTC activity, which is highly specific for OTC deficiency (PP4_Moderate, PMID: 10405441). The variant was not detected in the unaffected mother of this patient (PM6).
PS4_Supporting			This variant has been reported in 1 additional proband with biochemical and clinical evidence of OTC deficiency (PS4_Supporting; PMID: 25994866).
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			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
BS3			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

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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