

Variant: *NM_000531.6(OTC):c.814GAG[1] (p.Glu273del)*

Version: 1.0

CA224805 [↗](#)

97337 (ClinVar) [↗](#)

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

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

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

UUID: 8d018a7f-2fec-481b-8127-618dfcbd8368

Approved on: 2026/6/11

Published on: 2026/6/12

HGVS expressions

NM_000531.6:c.817_819delGAG

NM_000531.6:c.814GAG[1]

NM_000531.6:c.817_819del

NM_000531.6(OTC):c.814GAG[1] (p.Glu273del)

NC_000023.11:g.38408975_38408977del

CM000685.2:g.38408975_38408977del

NC_000023.10:g.38268228_38268230del

CM000685.1:g.38268228_38268230del

NC_000023.9:g.38153172_38153174del

NG_008471.1:g.61493_61495del

ENST00000039007.5:c.817_819del

ENST000000643344.1:c.*567_*569del

ENST00000039007.4:c.817_819del

ENST000000465127.1:c.172-257146_172-257144del

NM_000531.5:c.817_819del

Likely Pathogenic

Met criteria codes **4**

PM2_Supporting

PP4_Moderate

PS4_Moderate

PM4

Not Met criteria codes **5**

BS1

BP4

BP3

PP3

BA1

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.817_819del variant in OTC is predicted to cause a change in the length of the protein due to an in-frame deletion of 1 amino acid (p.Glu273del) in a non-repeat region (PM4). One male patient with this variant developed at 10 months of age hyperammonemic coma, and OTC enzymatic activity in liver tissue was reduced (5% wildtype) which is highly specific for OTC deficiency

(PP4_Moderate, PMID 8956045). This variant has been reported in 4 additional probands (3 male, 1 female) with biochemical and clinical evidence of OTC deficiency, with onset between 1.5 months and 18 years (PS4_Moderate; PMID: 34014557, 10799432, 17334707, 32420033). This variant has been reported not to segregate with clinical phenotype in two affected individuals from separate families, including a 64-year-old uncle of one proband and the older brother of another (BS4_Supporting; PMID 34014557, 32420033). The group max filtering allele frequency (Grpmax FAF) in gnomAD v4.1 is 3.800e-7 in European (non-Finnish) population, with 1 hemizygotes across all populations. This is lower than the ClinGen UCD VCEP threshold (<1.5e-5 AND ≤1 hemizygotes) for PM2_Supporting, meeting this criterion (PM2_Supporting). In summary, this variant meets the criteria to be classified as Likely Pathogenic for X-linked ornithine carbamoyltransferase deficiency. Although there are both pathogenic and benign types of evidence, this variant is associated with late-onset OTC deficiency, expression and penetrance may vary depending on environmental factors, and the absence of clinical phenotype in the individuals reported above is not considered inconsistent with the final classification. ACMG/AMP criteria applied, as specified by the ClinGen Urea Cycle Disorders VCEP (OTC specifications version 1.0.0), 02/09/2025: PM4, PP4_Moderate, PS4_Moderate, PM2_Supporting, BS4_Supporting.

Met criteria codes

PM2_Supporting			The group max filtering allele frequency (Grpmax FAF) in gnomAD v4.1 is 3.800e-7 in European (non-Finnish) population, with 1 hemizygote across all populations. This is lower than the ClinGen UCD VCEP threshold (<1.5e-5 AND ≤1 hemizygotes) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4_Moderate			One male patient with this variant developed hyperammonemic coma with 10 months of age. OTC enzymatic activity in liver tissue was reduced (5% wildtype) which is highly specific for OTC deficiency (PP4_Moderate, PMID 8956045).
PS4_Moderate			This variant has been reported in 4 additional probands with biochemical and clinical evidence of OTC deficiency (PS4_Moderate; PMID: 34014557, 10799432, 17334707, 32420033).
PM4			The NM_000531.6:c.817_819del variant in OTC is predicted to cause a change in the length of the protein due to an in-frame deletion of 1 amino acid (p.Glu273del) in a non-repeat region (PM4).

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			Review if PP3 is applicable for indels
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History		
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