The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000531.6(OTC):c.77G>A (p.Arg26Gln)

Version: 1.0

CA255647

10993 (ClinVar)

Gene: OTC (HGNC:5009)
Condition: ornithine carbamoyltransferase deficiency (MONDO:0010703)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: d294719e-66ab-463d-a95f-5954cfd78f89
Approved on: 2026/5/20
Published on: 2026/5/30

HGVS expressions

NM_000531.6:c.77G>A
NM_000531.6(OTC):c.77G>A (p.Arg26Gln)
NC_000023.11:g.38352773G>A
CM000685.2:g.38352773G>A
NC_000023.10:g.38212026G>A
CM000685.1:g.38212026G>A
NC_000023.9:g.38096970G>A
NG_008471.1:g.5291G>A
ENST00000039007.5:c.77G>A
ENST00000643344.1:c.77G>A
ENST00000039007.4:c.77G>A
ENST00000465127.1:c.172-313348G>A
ENST00000488812.1:n.169G>A
NM_000531.5:c.77G>A

Pathogenic

Met criteria codes 3

PM2_Supporting PP4_Moderate PS4

Not Met criteria codes 4

PP3 PM1 PM5 BP4

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_000156.6:c.77G>A variant in OTC is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 26 (p.Arg26Gln). This variant has been detected in at least 10 unrelated individuals with OTC deficiency (PMID: 17041896, PMID: 17334707, PMID: 23769969, PMID: 2474822* [counted for PP4], PMID: 25994866, PMID: 28266016, PMID: 32410394, PMID: 35281663). The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (PMID: 17041896, PMID:

17334707, PMID: 23769969, PMID: 2474822* [counted for PP4], PMID: 25994866, PMID: 28266016, PMID: 32410394) (PS4_VeryStrong). One of these individuals was a male who had deficient (<20% of wild-type) OTC enzyme activity in liver biopsy (PMID: 2474822) (2pts; PP4_Moderate). This variant is absent in gnomAD v4.1.0 (PM2_Supporting), though it is flagged as having low quality genotypes removed. The computational predictor REVEL gives a score of 0.562 which is neither above nor below the thresholds predicting a damaging (>0.75) or benign (<0.25) impact on OTC function. In summary, this variant meets the criteria to be classified as pathogenic for OTC deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Urea Cycle Disorders Variant Curation Expert Panel (OTC specifications version 1.0.0): PS4_VeryStrong, PP4_Moderate, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0 (PM2_Supporting).
PP4_Moderate	✔	One of the individuals detected was a male who showed hyperammonemia and deficient OTC enzyme activity in liver biopsy (PMID: 2474822) (2pts; PP4_Moderate)
PS4	✔	Detected in at least 10 unrelated individuals with OTC deficiency (9 counted for PS4 evidence, as 1 of these individuals [patient M, PMID: 2474822] counted for PP4 evidence), all of whom showed biochemical and/or clinical evidence of OTC deficiency phenotype (PMID: 17041896, PMID: 17334707, PMID: 23769969, PMID: 2474822* [counted for PP4], PMID: 25994866, PMID: 28266016, PMID: 32410394, PMID: 35281663)

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.562, which is between 0.644 and 0.290, evidence that correlates with uncertain impact on OTC function.
PM1	✖	Not at one of the critical regions of OTC as defined by the UCD VCEP specifications for OTC
PM5	✖	Two different missense variants in the same codon, p.Arg26Pro (ClinVar Variation ID: 97319) and p.Arg26Leu (ClinVar Variation ID: 1685390), have been reported pathogenic or likely pathogenic in ClinVar. Did not count for PM5 evidence to prevent circularity, as p.Arg26Gln will be used as evidence for PM5 for these variants.
BP4	✖	The computational predictor REVEL gives a score of 0.562, which is between 0.644 and 0.290, evidence that correlates with uncertain impact on OTC function.

Curation History

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