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Variant: NM_000531.6(OTC):c.589G>A (p.Gly197Arg)

Version: 1.0

CA224695

97260 (ClinVar)

Gene: OTC (HGNC:5009)
Condition: ornithine carbamoyltransferase deficiency (MONDO:0010703)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 5e3b72d9-7caf-43a8-80e6-bef9f130c347
Approved on: 2026/5/20
Published on: 2026/5/30

HGVS expressions

NM_000531.6(OTC):c.589G>A (p.Gly197Arg)
NM_000531.6:c.589G>A
NC_000023.11:g.38403666G>A
CM000685.2:g.38403666G>A
NC_000023.10:g.38262919G>A
CM000685.1:g.38262919G>A
NC_000023.9:g.38147863G>A
NG_008471.1:g.56184G>A
ENST00000039007.5:c.589G>A
ENST00000643344.1:c.*339G>A
ENST00000039007.4:c.589G>A
ENST00000465127.1:c.172-262455G>A
ENST00000488812.1:n.626G>A
NM_000531.5:c.589G>A

Likely Pathogenic

Met criteria codes 3

PP3_Strong | PM2_Supporting | PP4

Not Met criteria codes 1

PM5

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(OTC):c.589G>A variant in OTC is a missense variant predicted to cause substitution of Glycine by Arginine at amino acid 197(p.Gly197Arg). The computational predictor REVEL gives a score of 0.981, which is above the threshold of 0.932 and Strong evidence of impact on OTC function (PP3_Strong). One female patient with this variant displayed hyperammonemia, elevated orotic acid, and OTC enzyme activity from jejunal biopsy <25% (point score 1.0), which is highly specific for OTC deficiency (PP4_supporting, PMID: 10502831).

This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In summary, this variant meets the criteria to be classified as Likely 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): PP3_strong, PP4_supporting, PM2_supporting.

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.981, which is above the threshold of 0.932 and Strong evidence of impact on OTC function (PP3_Strong).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting)
PP4	✔	One female patient with this variant displayed hyperammonemia, elevated orotic acid, and OTC enzyme activity from jejunal biopsy <25% (point score 1.0), which is highly specific for OTC deficiency (PP4_supporting, PMID: 10502831).

Not Met criteria codes

PM5	✖	NM_000531.6(OTC):c.590G>A (p.Gly197Glu) is reported in ClinVar (97261) as pathogenic, but has not yet been curated by the ClinGen UCD VCEP.

Curation History

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