

Variant: *NM_000203.5(IDUA):c.64C>T (p.Pro22Ser)*

Version: 1.1

CA355945380 [↗](#)

553029 (ClinVar) [↗](#)

Gene: IDUA ([HGNC:3425](#))

Condition: mucopolysaccharidosis type 1 ([MONDO:0001586](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: b54443f4-7836-4921-9239-5f59afbaffde

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HGVS expressions

NM_000203.5(IDUA):c.64C>T (p.Pro22Ser)

NM_000203.5:c.64C>T

NC_000004.12:g.987148C>T

CM000666.2:g.987148C>T

NC_000004.11:g.980936C>T

CM000666.1:g.980936C>T

NC_000004.10:g.970936C>T

NG_008103.1:g.5152C>T

NG_033042.1:g.11289G>A

ENST00000247933.9:c.64C>T

ENST00000514224.2:c.64C>T

ENST00000247933.8:c.64C>T

ENST00000398520.6:c.576+3980G>A

ENST00000502910.5:c.64C>T

ENST00000504568.5:c.62C>T

ENST00000506561.5:n.73C>T

ENST00000508168.5:n.83C>T

ENST00000514698.5:n.105C>T

ENST00000622731.4:c.576+3980G>A

NM_000203.4:c.64C>T

NM_134425.2:c.576+3980G>A

NR_110313.1:n.152C>T

NM_134425.3:c.576+3980G>A

NM_134425.4:c.576+3980G>A

Uncertain Significance

Met criteria codes **3**

PM2_Supporting PP3 PP4

Not Met criteria codes **1**

PM3

Evidence Links **0**

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Lysosomal Diseases
Expert Panel Specifications to the ACMG/AMP Variant
Interpretation Guidelines for IDUA Version 1.2.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Lysosomal Diseases VCEP

The NM_000203.5:c.64C>T variant in IDUA is a missense variant predicted to cause substitution of proline by serine at amino acid 22 (p.Pro22Ser). At least one patient with this variant found to be compound heterozygous in documented IDUA deficiency within the affected range in leukocytes [α -Iduronidase enzyme activity 0.01 nmol/21 h*punch] and clinical features specific to MPS I including coarse facial features, hepatosplenomegaly, corneal clouding, gibbus, developmental delay, short stature, frequent respiratory illness and/or umbilical hernia (PP4). One patient compound heterozygous for c.64C>T (p.Pro22Ser) and another variant that has not yet been classified as pathogenic or likely pathogenic by the ClinGen LD VCEP, c.1829-1G>A; phase unknown (PM3 is not met). The highest population minor allele frequency in gnomAD v4.0. is 9.167e-7 (1/1090820 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.692 which is in the range 0.644-0.773, evidence that correlates with impact to IDUA function at the supporting level (PP3; PMID: 36413997). There is a ClinVar entry for this variant (Variation ID: 553029). In summary, this variant meets the criteria to be classified as variant of uncertain significance for MPS I based on the IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 1.2.0): PP4, PP3, PM2_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on January 5, 2026)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.0. is 9.167e-7 (1/1090820 alleles) in the European - Non Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).
PP3			The computational predictor REVEL gives a score of 0.692 which is in the range 0.644-0.773, evidence that correlates with impact to IDUA function at the supporting level (PMID: 36413997) (PP3).
PP4			One individual with this variant has been reported with clinical symptoms consistent with MPS I and IDUA activity in the affected range in dried blood spots (PMID:24798265) (PP4).

Not Met criteria codes

PM3			One patient compound heterozygous for c.64C>T (p.Pro22Ser) and another variant that has not yet been classified as pathogenic or likely pathogenic by the ClinGen LD VCEP, c.1829-1G>A; phase unknown. (PM3 is not met).
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