

Variant: *NM_000203.5(IDUA):c.895G>T (p.Glu299Ter)*

Version: 1.0

CA355962511 [↗](#)

987878 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 827b53ba-aaa5-414e-93ca-377fab47a169

Approved on: 2025/6/16

Published on: 2025/7/18

HGVS expressions

NM_000203.5(IDUA):c.895G>T (p.Glu299Ter)

NM_000203.5:c.895G>T

NC_000004.12:g.1002084G>T

CM000666.2:g.1002084G>T

NC_000004.11:g.995872G>T

CM000666.1:g.995872G>T

NC_000004.10:g.985872G>T

NG_008103.1:g.20088G>T

ENST00000247933.9:c.895G>T

ENST00000514224.2:c.895G>T

ENST00000652070.1:n.951G>T

ENST00000247933.8:c.895G>T

ENST00000514224.1:c.499G>T

ENST00000514698.5:n.895G>T

NM_000203.4:c.895G>T

NR_110313.1:n.983G>T

NM_001363576.1:c.499G>T

Pathogenic

Met criteria codes **4**

PM2_Supporting

PVS1

PP4

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 1.0.0*

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

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5(IDUA):c.895G>T (p.Glu299Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant exon 7 out of 14, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). At least 2 patients with this variant had documented IDUA deficiency within the affected range in leukocytes and clinical features specific to MPS I including dysostosis multiplex, hepatosplenomegaly, arthropathy, and corneal involvement (PMIDs: 16438163, 27146977) (PP4). Of those individuals, one was compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP, c.223G>A (p.Ala75Thr) (ClinVar Variation ID: 222993); the phase was not confirmed (0.5 points; PMID: 27146977). One individual was homozygous for the variant (ClinVar SCV002562742.2) (0.5 points). Total 1 point (PM3). Another patient was compound heterozygous for the variant and c.164dup (PMID: 16438163). The allelic data for this patient will be used to support the classification of c.164dup and is not included here in order to avoid circular logic. The highest population minor allele frequency in gnomAD v4.1.0. is 0.000023 (2/86636 alleles) in the South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 987878). In summary, this variant meets the criteria to be classified as pathogenic 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 1.0.0): PVS1, PP4, PM3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on June 16, 2025)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 0.000023 (2/86636 alleles) in the South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).
PVS1			The NM_000203.5(IDUA):c.895G>T (p.Glu299Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant exon 7 out of 14, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP4			At least 2 patients with this variant had documented IDUA deficiency within the affected range in leukocytes and clinical features specific to MPS I including dysostosis multiplex, hepatosplenomegaly, arthropathy, and corneal involvement (PMIDs: 16438163, 27146977) (PP4).
PM3			This variant has been detected in at least 2 individuals with MPS I. Of those individuals, 1 was compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP, c.223G>A (p.Ala75Thr) (ClinVar Variation ID: 222993); the phase was not confirmed (0.5 points; PMID: 27146977). One individual was homozygous for the variant (ClinVar SCV002562742.2) (0.5 points). Total 1 point (PM3). Another patient was compound heterozygous for the variant and c.164dup (PMID: 16438163). The allelic data for this patient will be used to support the classification of c.164dup and is not included here in order to avoid circular logic.

Curation History 

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