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Variant: NM_000203.5(IDUA):c.159C>A (p.Cys53Ter)

Version: 1.0

CA355945972

1458768 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 14aa365c-849a-4ced-a37b-fbb2c811539f
Approved on: 2025/10/20
Published on: 2025/12/5

HGVS expressions

NM_000203.5(IDUA):c.159C>A (p.Cys53Ter)
NM_000203.5:c.159C>A
NC_000004.12:g.987809C>A
CM000666.2:g.987809C>A
NC_000004.11:g.981597C>A
CM000666.1:g.981597C>A
NC_000004.10:g.971597C>A
NG_008103.1:g.5813C>A
NG_033042.1:g.10628G>T
ENST00000247933.9:c.159C>A
ENST00000398516.3:c.*1024G>T
ENST00000514224.2:c.159C>A
ENST00000247933.8:c.159C>A
ENST00000361661.6:c.*1024G>T
ENST00000398520.6:c.576+3319G>T
ENST00000502910.5:c.158+567C>A
ENST00000504568.5:c.157C>A
ENST00000506561.5:n.168C>A
ENST00000508168.5:n.177+567C>A
ENST00000514698.5:n.199+567C>A
ENST00000622731.4:c.576+3319G>T
NM_000203.4:c.159C>A
NM_022042.3:c.*1024G>T
NM_134425.2:c.576+3319G>T
NM_213613.3:c.*1024G>T
NR_110313.1:n.247C>A
NM_022042.4:c.*1024G>T
NM_134425.3:c.576+3319G>T
NM_213613.4:c.*1024G>T
NM_134425.4:c.576+3319G>T

Pathogenic

Met criteria codes 3

PVS1 PM2_Supporting PP4_Moderate

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 1.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5: c.159C>A (p.Cys53Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2 out of 14, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). Three patients with a diagnosis of MPS I have been reported to be compound heterozygous for the variant and either c.546G>C (p.Glu182Asp) (PMID: 21480867), c.1037T>G (p.Leu346Arg) (PMID: 21480867) or c.653T>C (p.Leu218Pro) (PMID: 34547335). The allelic data from the patients will be used in the classification of the second variant and is not included here to avoid circular logic. Two of these patients had documented IDUA deficiency within the affected range in leukocytes, and urinary GAGs expressed as either total GAGs or specific GAG elevation above normal range. One patient is reported with clinical features specific to MPS I (Hurler) including global developmental delay, macrocephaly, joint stiffness, Mongolian maculae, hepatosplenomegaly, hernia, with a Hurler-Sheie phenotype (PMID: 21480867) (PP4_moderate). This variant is absent in gnomAD v4.0. (PM2_Supporting). There is a ClinVar entry for the variant (Variation ID: 1458768). 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 1.1.0): PVS1, PP4, PM2_Supporting (Classification approved by the Clingen Lysosomal Diseases Variant Curation Expert Panel on October 20, 2025)

Met criteria codes

PVS1	✔	The NM_000203.5: c.159C>A (p.Cys53Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2 out of 14, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).
PP4_Moderate	✔	At least 2 patients with this variant had documented IDUA deficiency within the affected range in leukocytes, and urinary GAGs expressed as either total GAGs or specific GAG elevation above normal range. One patient is reported with clinical features specific to MPS I (Hurler) including global developmental delay, macrocephaly, joint stiffness, Mongolian maculae, hepatosplenomegaly, hernia, with a Hurler-Sheie phenotype (PMID: 21480867, 34547335) (PP4_moderate).

Not Met criteria codes

PM3	✖	Three patients with a diagnosis of MPS I have been reported to be compound heterozygous for the variant and either c.546G>C (p.Glu182Asp) (PMID: 21480867), c.1037T>G (p.Leu346Arg) (PMID: 21480867) or c.653T>C

(p.Leu218Pro) (PMID: 34547335). The allelic data from the patients will be used in the classification of the second variant and is not included here to avoid circular logic.

Curation History

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