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Variant: NM_000203.5(IDUA):c.236C>T (p.Ala79Val)

Version: 2.0

CA356987

1458769 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: da5189c2-5507-488f-b202-b7e8bd60fb5e
Approved on: 2026/5/4
Published on: 2026/5/14

HGVS expressions

NM_000203.5(IDUA):c.236C>T (p.Ala79Val)
NM_000203.5:c.236C>T
NC_000004.12:g.987886C>T
CM000666.2:g.987886C>T
NC_000004.11:g.981674C>T
CM000666.1:g.981674C>T
NC_000004.10:g.971674C>T
NG_008103.1:g.5890C>T
NG_033042.1:g.10551G>A
ENST00000247933.9:c.236C>T
ENST00000398516.3:c.*947G>A
ENST00000514224.2:c.236C>T
ENST00000247933.8:c.236C>T
ENST00000361661.6:c.*947G>A
ENST00000398520.6:c.576+3242G>A
ENST00000502910.5:c.158+644C>T
ENST00000504568.5:c.234C>T
ENST00000506561.5:n.245C>T
ENST00000508168.5:n.177+644C>T
ENST00000514698.5:n.199+644C>T
ENST00000622731.4:c.576+3242G>A
NM_000203.4:c.236C>T
NM_022042.3:c.*947G>A
NM_134425.2:c.576+3242G>A
NM_213613.3:c.*947G>A
NR_110313.1:n.324C>T
NM_022042.4:c.*947G>A
NM_134425.3:c.576+3242G>A
NM_213613.4:c.*947G>A
NM_134425.4:c.576+3242G>A

Pathogenic

Met criteria codes 5

PP3 | PM3_Very Strong | PP4_Moderate | PM2_Supporting | PS3_Supporting

Not Met criteria codes 2

PM1 | PM5

Evidence Links 1

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**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5(IDUA):c.236C>T variant in IDUA is a missense variant predicted to cause substitution of Alanine by Valine at amino acid 79 (p.Ala79Val). At least 1 patient with this variant had documented IDUA deficiency within the affected range in leukocytes, urinary GAGs elevation above normal range, and clinical features specific to MPS I including hepatosplenomegaly, arthropathy, and corneal involvement (PP4). This variant has been detected in at least 11 individuals with MPS I. Of those individuals, 3 were compound heterozygous, phase confirmed in trans by parental testing, for the variant and a variant in IDUA that has been classified as likely pathogenic or pathogenic by the ClinGen LD VCEP (variants: c.1037T>G (p.Leu346Arg, ClinVar Variation ID: 11927), c.1877G>A (p.Trp626Ter, ClinVar Variation ID: 928997) and c.1402+1G>T (ClinVar Variation ID: 1323099) (3 x 1.0 points = 3.0 points). Another five individuals are compound heterozygous for the variant and a variant in IDUA, either c.536C>G (p.Thr179Arg) (ClinVar Variation ID: 556358), c.589G>A (p.Val197Ile) (ClinVar Variation ID: 2720835), c.265C>T (p.Arg89Trp) (ClinVar Variation ID: 580286), or c.1037T>G (p.Leu346Arg) (ClinVar Variation ID: 11927) (PMIDs: 27520059, 21480867). The allelic data from these individuals will be used in the assessment of the second variant. Three individuals were homozygous for the variant (1 point; PMID: 21480867). Total 4.0 points (PM3_VeryStrong). This variant is absent in gnomAD v4.1.0 (PM2_Supporting). Expression of the variant in CHO-cells resulted in less than 0.1% wild type IDUA activity indicating that this variant may impact protein function (PMID:15300847)(PS3_Supporting). The computational predictor REVEL gives a score of 0.738 which is in the range 0.644-0.773, evidence that correlates with impact to IDUA function at the supporting level (Pejaver et al.) (PP3). Another missense variant c.235G>A (p.Ala79Thr) in the same codon has not yet been reported in a patient with MPS I. Additionally, this other variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen LD VCEP (PM5 not met). There is a ClinVar entry for this variant (Variation ID: 1458769). 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 1.2.0): PP4, PM3_VeryStrong, PM2_Supporting, PS3_Supporting, PP3 (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 4, 2026)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.738 which is in the range 0.644- 0.773, evidence that correlates with impact to IDUA function at the supporting level (Pejaver et al.) (PP3).
PM3_Very Strong	✔	This variant has been detected in at least 11 individuals with MPS I. Of those individuals, 3 were compound heterozygous, phase confirmed in trans by parental testing, for the variant and a variant in IDUA that has been classified as likely pathogenic or pathogenic by the ClinGen LD VCEP (variants: c.1037T>G (p.Leu346Arg, ClinVar Variation ID: 11927), c.1877G>A (p.Trp626Ter, ClinVar Variation ID: 928997) and c.1402+1G>T (ClinVar Variation ID: 1323099) (3 x 1.0 points = 3.0 points). Another five individuals are compound heterozygous for the variant and a variant in IDUA, either c.536C>G (p.Thr179Arg) (ClinVar Variation ID: 556358), c.589G>A (p.Val197Ile) (ClinVar Variation ID: 2720835), c.265C>T (p.Arg89Trp) (ClinVar Variation ID: 580286), or c.1037T>G (p.Leu346Arg) (ClinVar Variation ID: 11927) (PMIDs: 27520059, 21480867). The allelic data from these individuals will be used in the

assessment of the second variant. Three individuals were homozygous for the variant (1 point; PMID: 21480867).
Total 4.0 points (PM3_VeryStrong).

PP4_Moderate	✔	At least 2 patients with this variant had documented IDUA deficiency within the affected range in leukocytes, urinary GAGs elevation above normal range, and clinical features specific to MPS I including hepatosplenomegaly, and corneal involvement (PMID: 27520059; PP4_Moderate).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0 (PM2_Supporting). (Note that a variant with the same protein change occurs on a different IDUA transcript is listed in gnomAD v4.1.0.)
PS3_Supporting	✔	Expression of the variant in CHO cells and COS-7 cells resulted in less than 0.1% and 0.4%, respectively, of wild type IDUA activity indicating that this variant may impact protein function (PMIDs: 15300847, 12189649; PS3_Supporting) Expression of the variant in COS-7 cells resulted in less than 0.4% wild type IDUA activity indicating that this variant may impact protein function (PMID:12189649)(PS3_Supporting) PubMed:12189649

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	Another missense variant, c.235G>A (p.Ala79Thr), in the same codon has been classified as benign.

Curation History

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