

Variant: *NM_000203.5(IDUA):c.590G>A (p.Gly197Asp)*

Version: 1.0

CA91167598 [↗](#)

554670 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: fa1dcac4-03bb-478f-abc1-32be14c13626

Approved on: 2025/11/3

Published on: 2025/12/28

HGVS expressions

NM_000203.5:c.590G>A

NM_000203.5(IDUA):c.590G>A (p.Gly197Asp)

NC_000004.12:g.1001679G>A

CM000666.2:g.1001679G>A

NC_000004.11:g.995467G>A

CM000666.1:g.995467G>A

NC_000004.10:g.985467G>A

NG_008103.1:g.19683G>A

ENST00000247933.9:c.590G>A

ENST00000514224.2:c.590G>A

ENST00000652070.1:n.646G>A

ENST00000247933.8:c.590G>A

ENST00000502910.5:c.449G>A

ENST00000504568.5:c.550G>A

ENST00000509948.5:c.383G>A

ENST00000514192.5:c.407G>A

ENST00000514224.1:c.194G>A

ENST00000514698.5:n.490G>A

NM_000203.4:c.590G>A

NR_110313.1:n.678G>A

NM_001363576.1:c.194G>A

Likely Pathogenic

Met criteria codes **4**

PM2_Supporting

PM3

PP4

PVS1_Strong

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**

Lysosomal Diseases VCEP

NM_000203.5(IDUA):c.590G>A: variant in IDUA is a missense variant in exon 6, predicted to cause substitution of glycine by aspartate at amino acid 197, p.Gly197Asp. The variant has been reported in at least two probands with MPS I (PMID: 32188113, 12203999, 39754079). Both of these individuals are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP, including c.1598C>G (p.Pro533Arg) (ClinVar Variation ID: 11910) (PMID: 32188113, 12203999: PM3, 0.5 points, phase unknown) and c.1139dup (PMID: 39754079, trans confirmed, 1 point) (total 1.5 points, PM3). One has an attenuated phenotype and is part of a cohort in which the diagnosis was “based on the clinical features, excessive urinary glycosaminoglycan excretion, and reduced IDUA activity in fibroblasts and/or leukocytes (PMID: 12203999). The second is a fetus terminated at 35GW, which showed signs of MPS 1. Ultrasound examination at 24.0 GW revealed hepatosplenomegaly and dysmorphic features, including a long, broad philtrum, as well as echogenic spots in the liver, spleen, peritoneum, and thymus. IDUA activity in cultured amniocytes was deficient (0.3 µkat/kg normal 33.8 µkat/kg). Placenta analysis showed a single umbilical artery and a microvacuolized appearance of Hofbauer cells, compatible with lysosomal overload (PMID: 39754079) (PP4_Supporting). Of note, another variant, c.494-57G>A, was found to be in cis with c.590G>A in the affected fetus. The c.590G>A variant in IDUA alters the first nucleotide of exon 6. A minigene assay revealed that the variant results in a major transcript with complete retention of intron 5, as well as several alternative transcripts with retention of the last 22, 25 and 28 nucleotides of intron 5. Complete retention of intron 5 leads to a premature stop codon, p.Phe198ValfsTer127 (PMID: 39754079) (PVS1_Strong). Note that the SpliceAI score for acceptor loss for c.590G>A is 0.19 (just below the required threshold of >0.2 for prediction of splice impact). PVS1 (Very strong) was not used because the mini gene assay results were missing from the publication. The highest population minor allele frequency in gnomAD v4.1.0 is 0.000007633 (9/1179014 alleles) in the European (non-Finnish) genetic ancestry group; this is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.00025), due to which we can apply PM2_Supporting. There is a ClinVar entry for this variant (Variation ID: 554670). In summary, this variant meets the criteria to be classified as Likely Pathogenic for MPS1 based on the IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Disease Variant Curation Expert Panel (Specifications Version 1.1.0): PVS1_Strong, PM3, PP4, PM2_Supporting (Classification approved by the ClinGen Lysosomal Disease Variant Curation Expert Panel on November 3, 2025)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in GnomAD v4.1 is 0.000007633 (9/1179014 alleles) in the European (non-Finnish) genetic ancestry group; this is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.00025) due to which we can apply PM2_Supporting.
PM3			The variant has been reported in at least two probands with MPS 1(PMID: 32188113, 12203999, 39754079). Both of these individuals are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP, including c.1598C>G (p.Pro533Arg) (ClinVar Variation ID: 11910) (PMID: 32188113, 12203999: PM3, 0.5 points, phase unknown) and c.1139dup (PMID: 39754079, trans confirmed, 1 point) (total 1.5 points, PM3_Moderate)
PP4			The variant has been reported in at least two probands with MPS 1(PMID: 32188113, 12203999, 39754079). One has an attenuated phenotype and is part of a cohort in which the diagnosis was “based on the clinical features, excessive urinary glycosaminoglycan excretion, and reduced IDUA activity in fibroblasts and/or leukocytes (PMID: 12203999). The second is a fetus terminated at 35GW, which showed signs of MPS 1. Ultrasound examination at 24.0 GW revealed hepatosplenomegaly and dysmorphic features, including a long, broad philtrum, as well as echogenic spots in the liver, spleen, peritoneum, and thymus. IDUA activity in cultured amniocytes was deficient (0.3 µkat/kg normal 33.8 µkat/kg). Placenta analysis showed a single umbilical artery and a microvacuolized appearance of Hofbauer cells, compatible with lysosomal overload (PMID: 39754079) (PP4_Supporting). Of note, another variant, c.494-57G>A, was found to be in cis with c.590G>A in the affected fetus.

PVS1_Strong

The c.590G>A variant in IDUA alters the first nucleotide of exon 6. A minigene assay revealed that the variant results in a major transcript with complete retention of intron 5, as well as several alternative transcripts with retention of the last 22, 25 and 28 nucleotides of intron 5. Complete retention of intron 5 leads to a premature stop codon, p.Phe198ValfsTer127 (PMID: 39754079) (PVS1_Strong). Note that the SpliceAI score for acceptor loss for c.590G>A is 0.19 (just below the required threshold of >0.2 for prediction of splice impact). PVS1_Very strong was not used because the mini gene assay results were missing from the publication.

Curation History

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