The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000203.5(IDUA):c.590-7G>A

Version: 1.0

CA356990

222996 (ClinVar)

Gene: IDUA
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: b97d1371-e9cc-45bc-9b2b-fb9084c93edc
Approved on: 2024-12-06
Published on: 2025-06-07

HGVS expressions

NM_000203.5:c.590-7G>A
NM_000203.5(IDUA):c.590-7G>A
NC_000004.12:g.1001672G>A
CM000666.2:g.1001672G>A
NC_000004.11:g.995460G>A
CM000666.1:g.995460G>A
NC_000004.10:g.985460G>A
NG_008103.1:g.19676G>A
ENST00000247933.9:c.590-7G>A
ENST00000514224.2:c.590-7G>A
ENST00000652070.1:n.646-7G>A
ENST00000247933.8:c.590-7G>A
ENST00000502910.5:c.449-7G>A
ENST00000504568.5:c.550-7G>A
ENST00000509948.5:c.383-7G>A
ENST00000514192.5:c.407-7G>A
ENST00000514224.1:c.194-7G>A
ENST00000514698.5:n.490-7G>A
NM_000203.4:c.590-7G>A
NR_110313.1:n.678-7G>A
NM_001363576.1:c.194-7G>A

Pathogenic

Met criteria codes 4

PM3_Strong PM2_Supporting PP4_Moderate 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 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5: c.590-7G>A variant in IDUA occurs within the splice acceptor site motif of intron 5. RT-PCR analysis revealed skipping of biologically-relevant-exon 6/14, or, rarely, intron 5 inclusion, resulting mainly in splicing at nt -28 of intron 5, and also a very small amount of normal IDUA mRNA (PMID: 8213840; 9748610) (PVS1_Strong (RNA)). This variant is also reported as IDUA:c. 678-7 G>A in older literature (PMID: 8213840). This variant has been detected in at least 10 individuals with MPS I, all compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP, all phase unconfirmed, including c.208C>T (p.Gln70Ter) (PMID: 28752568, ClinVar Variation ID: 11909, 0.5 points), c.1205G>A (p.Trp402Ter) (PMID: 28752568, CinVar Variation ID: 11908, 7 patients, max 2 x 0.5 points), and (c.1029C>G (p.Tyr343Ter) (C;inVar Variation ID: 550474, clinical lab, 0.5 points) (PM3_Strong). Total 2 points (PM3_Strong). At least 1 patient with this variant had documented IDUA deficiency within the affected range in leukocytes, a significant reduction in urine GAGs upon treatment with enzyme replacement therapy, and clinical features specific to MPS I including arthropathy, corneal involvement, and valvular thickening. (PP4_Moderate). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00004241 (50/1178952 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). There is a ClinVar entry for this variant (Variation ID: 222996). 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_strong, PM3_strong, PP4_moderate, PM2_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 6, 2024)

Met criteria codes

PM3_Strong ✔	This variant has been detected in at least 10 individuals with MPS I, all compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP, all phase unconfirmed, including c.208C>T (p.Gln70Ter) (PMID: 28752568, ClinVar Variation ID: 11909, 0.5 points), c.1205G>A (p.Trp402Ter) (PMID: 28752568, CinVar Variation ID: 11908, 7 patients, max 2 x 0.5 points), and (c.1029C>G (p.Tyr343Ter) (C;inVar Variation ID: 550474, clinical lab, 0.5 points) (PM3_Strong). Total 2 points (PM3_Strong).
PM2_Supporting ✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00004241 (50/1178952 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).
PP4_Moderate ✔	At least 1 patient with this variant had documented IDUA deficiency within the affected range in leukocytes, a significant reduction in urine GAGs upon treatment with enzyme replacement therapy, and clinical features specific to MPS I including arthropathy, corneal involvement, and valvular thickening. (PP4_Moderate).
PVS1_Strong ✔	The NM_000203.5: c.590-7G>A variant in IDUA occurs within the splice acceptor site motif of intron 5. RT-PCR analysis revealed skipping of biologically-relevant-exon 6/14, or, rarely, intron 5 inclusion, resulting mainly in splicing at nt -28 of intron 5, and also a very small amount of normal IDUA mRNA (PMID: 8213840; 9748610) (PVS1_Strong (RNA)).

Curation History