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.539G>C (p.Trp180Ser)

Version: 1.0

CA91167249

1021968 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: c30198e0-71c5-423a-bd45-8690ae0bbc58
Approved on: 2025/5/7
Published on: 2025/5/7

HGVS expressions

NM_000203.5(IDUA):c.539G>C (p.Trp180Ser)
NM_000203.5:c.539G>C
NC_000004.12:g.1001513G>C
CM000666.2:g.1001513G>C
NC_000004.11:g.995301G>C
CM000666.1:g.995301G>C
NC_000004.10:g.985301G>C
NG_008103.1:g.19517G>C
ENST00000247933.9:c.539G>C
ENST00000514224.2:c.539G>C
ENST00000652070.1:n.595G>C
ENST00000247933.8:c.539G>C
ENST00000502910.5:c.398G>C
ENST00000504568.5:c.499G>C
ENST00000509948.5:c.332G>C
ENST00000514192.5:c.356G>C
ENST00000514224.1:c.143G>C
ENST00000514698.5:n.439G>C
NM_000203.4:c.539G>C
NR_110313.1:n.627G>C
NM_001363576.1:c.143G>C

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PM3 PP4 PP3_Moderate

Not Met criteria codes 3

PM1 PM5 PS1

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

NM_000203.5:c.539G>C IDUA variant is a missense variant predicted to cause substitution of tryptophan by serine at amino acid 180 (p.Trp180Ser). This variant has been detected in at least four probands with MPS I. Of these individuals, three are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic or likely pathogenic for MPS I by the ClinGen LD VCEP; all phase unconfirmed. The second variant was either c.46_57del (p.Ser16_Ala19del) (P by LD VCEP, Clinical Lab, 0.5 points), c.1861C>T (p.Arg621Ter) (LP by LD VCEP, Clinical Lab, 0.25 points), or c.1205G>A (p.Trp402Ter) (P by LD VCEP, PMID: 22976768, 25098213, possibly the same patient in both publications, 0.5 points). One individual is homozygous for the variant (Clinical Lab, 0.5 points). Total 1.75 points (PM3). At least one proband had reported deficiency of IDUA enzyme activity, and urinary dermatan and heparan sulfate elevation above normal range (PMID: 25098213; PMID: 22976768, Clinical Lab) (PP4). The highest population minor allele frequency in Genomes gnomAD v4.1.0 is 0.00001666 (1/60010 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025) (PM2_Supporting). The computational predictor REVEL gives a score of 0.959 which is above the threshold of 0.773, evidence that correlates with impact to IDUA function at the moderate level based on the specifications of the ClinGen Lysosomal Diseases VCEP (PMID: 36413997) (PP3_Moderate). There is a ClinVar entry for this variant (Variation ID:1021968). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Mucopolysaccharidosis type I. IDUA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP (Specifications Version 1.0.0.): PM3, PP3_moderate, PP4, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 7, 2025)

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in Genomes gnomAD v4.1.0 is 0.00001666 (1/60010 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025) (PM2_Supporting).
PM3	✔	This variant has been detected in at least four probands with MPS I. Of these individuals, are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic or likely pathogenic for MPS I by the ClinGen LD VCEP; all phase unconfirmed. The second variant was either c.46_57del (p.Ser16_Ala19del) (P, Clinical Lab, 0.5 points), c.1861C>T (p.Arg621Ter) (LP, Clinical Lab, 0.25 points), c.1205G>A (p.Trp402Ter) (PMID: 22976768, 25098213, possibly the same patient in both publications, 0.5 points). One individual is homozygous for the variant (Clinical Lab, 0.5 points). Total 1.75 points (PM3).
PP4	✔	At least one proband had reported deficiency of IDUA enzyme activity, and urinary dermatan and heparan sulfate elevation above normal range (PMID: 25098213; PMID: 22976768, Clinical Lab) (PP4).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.959 which is above the threshold of 0.773, evidence that correlates with impact to IDUA function at the moderate level based on the specifications of the ClinGen Lysosomal Diseases VCEP (PMID: 36413997) (PP3_Moderate).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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