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Variant: NM_000203.5(IDUA):c.956C>T (p.Ala319Val)

Version: 1.0

CA2802126

1683230 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 36f5b707-fb05-4fe2-8fc2-8494a52a3188
Approved on: 2025/8/8
Published on: 2025/9/16

HGVS expressions

NM_000203.5:c.956C>T
NM_000203.5(IDUA):c.956C>T (p.Ala319Val)
NC_000004.12:g.1002145C>T
CM000666.2:g.1002145C>T
NC_000004.11:g.995933C>T
CM000666.1:g.995933C>T
NC_000004.10:g.985933C>T
NG_008103.1:g.20149C>T
ENST00000247933.9:c.956C>T
ENST00000514224.2:c.956C>T
ENST00000652070.1:n.1012C>T
ENST00000247933.8:c.956C>T
ENST00000514224.1:c.560C>T
ENST00000514698.5:n.956C>T
NM_000203.4:c.956C>T
NR_110313.1:n.1044C>T
NM_001363576.1:c.560C>T

Likely Pathogenic

Met criteria codes 5

PP3_Moderate | PM3_Supporting | PP4 | PM2_Supporting | PS3_Supporting

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 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5:c.956C>T variant in IDUA is a missense variant predicted to cause substitution of alanine by valine at amino acid 319 (p.Ala319Val). One patient from Pakistan, homozygous for the variant, was diagnosed with attenuated MPS I (described as having Scheie syndrome) and low IDUA activity (PMID: 11735025) (PP4, PM3_supporting). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001673 (1/5976 alleles) in the Middle Eastern population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). When expressed in COS cells, the activity of the variant was indistinguishable from that of untransfected COS cells (PMID: 11735025) (PS3_Supporting). The computational predictor REVEL gives a score of 0.896 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: 1683230). In summary, this variant meets the criteria to be classified as likely pathogenic for mucopolysaccharidosis type I based on the IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Expert Panel (Specifications Version 1.0.0): PP3_Moderate, PP4, PS3_Supporting, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Expert Panel, August 8, 2025)

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.896 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). SpliceAI predicts that the variant has no impact on splicing.
PM3_Supporting	✔	This variant has been detected in at least 01 individuals with MPS I. This individual was homozygous for the variant (0.5 points, PMID: 11735025) (PM3_supporting).
PP4	✔	One patient from Pakistan, homozygous for the variant, was diagnosed with attenuated MPS I (described as having Scheie syndrome) and low IDUA activity (PMID: 11735025) (PP4)
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001673 (1/5976 alleles) in the Middle Eastern population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).
PS3_Supporting	✔	When expressed in COS cells, the activity of the variant was indistinguishable from that of untransfected COS cells (PMID: 11735025) (PS3_Supporting).

Table 8. When expressed in COS cells the IDUA activity of the variant is 5.2 nmol/h/mg cell protein. This is equal to the IDUA activity in COS cells alone (5.2 nmol/h/mg cell protein). The negative control (empty vector) has activity of 4.2 nmol/h/mg cell protein. Activity of WT IDUA expressed in COS cells is 88.1 nmol/h/mg cell protein. Although the cDNA change for this variant was not explicitly stated, it was confirmed from the primer sequences used for site-directed mutagenesis (see Table 4) PubMed:11735025

Curation History



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