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Variant: NM_001363576.1:c.547G>T

Version: 1.0

CA355962740

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 731cf73d-0281-435e-ab0c-2d4de4baa4c2
Approved on: 2025/12/15
Published on: 2025/12/28

HGVS expressions

NM_001363576.1:c.547G>T
NC_000004.12:g.1002132G>T
CM000666.2:g.1002132G>T
NC_000004.11:g.995920G>T
CM000666.1:g.995920G>T
NC_000004.10:g.985920G>T
NG_008103.1:g.20136G>T
ENST00000247933.9:c.943G>T
ENST00000514224.2:c.943G>T
ENST00000652070.1:n.999G>T
ENST00000247933.8:c.943G>T
ENST00000514224.1:c.547G>T
ENST00000514698.5:n.943G>T
NM_000203.4:c.943G>T
NR_110313.1:n.1031G>T
NM_000203.5:c.943G>T

Likely Pathogenic

Met criteria codes 5

PP4 PM3 PP3_Moderate PM2_Supporting PS3_Supporting

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5:c.943G>T variant in IDUA is a missense variant resulting in substitution of aspartate by tyrosine p.(Asp315Tyr). The variant has been detected in at least two probands with MPS I (PMIDs: 19396826, 24480078, 8680403, 29906569). One patient is reported

to have clinical features consistent with severe MPS I (Hurler syndrome) including short stature, macrocephaly, joint stiffness, delayed mental development, hepatosplenomegaly, umbilical hernia, progressive deafness, dysostosis multiplex, and corneal clouding. The diagnosis "was confirmed biochemically" by increased urine dermatan and heparan sulfate and deficiency IDUA activity,; however, no values were provided (PMID: 19396826) (PP4). This individuals is compound heterozygous for the variant and a second variant that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.208C>T (p.Gln70Ter) (PMIDs: 19396826, 24480078, 8680403); confirmed in trans (1 point) (PM3). The second proband is compound heterozygous for the variant and c.653T>C (p.Leu218Pro) (PMID: 29906569). The allelic data from this patient may be used in the classification of p.Leu218Pro and is not included here to avoid circular logic. The variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.82, which is above the threshold of 0.773, providing evidence that correlates with impact on IDUA function at the moderate level, based on the specifications of the ClinGen Lysosomal Diseases VCEP (PMID: 36413997) (PP3_Moderate). When transiently expressed in CHO cells, the variant resulted in <1% activity compared to wild type (PMID: 19396826 (PS3_Supporting). In summary, this variant meets the criteria to be classified as Likely Pathogenic for MPS I 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): PM3, PP3_Moderate, PP4, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Disease Variant Curation Expert Panel on December 15, 2025)

Met criteria codes

PP4	✔	One patient has been reported with clinical features consistent with severe MPS I (Hurler syndrome) including short stature, macrocephaly, joint stiffness, delayed mental development, hepatosplenomegaly, umbilical hernia, progressive deafness, dysostosis multiplex, and corneal clouding. The diagnosis "was confirmed biochemically" by increased urine dermatan and heparan sulfate and deficiency IDUA activity,; however, no values were provided (PMID: 19396826) (PP4).
PM3	✔	One proband is compound heterozygous for this variant and a second variant that has been classified as pathogenic or likely pathogenic by the ClinGen Lysosomal Diseases VCEP, including c.208C>T (p.Gln70Ter, p.Q70X) (PMIDs: 19396826, 24480078). PMID:24480078 reports p.Q70X is on the other allele (PM3_Moderate, 1 patient, phase known, 1 point)
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.82, which is above the threshold of 0.773, providing evidence that correlates with impact on IDUA function at the moderate level, based on the specifications of the ClinGen Lysosomal Diseases VCEP (PMID: 36413997) (PP3_Moderate).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).
PS3_Supporting	✔	The α-L-Iduronidase activity for c.943G>T was measured in CHO cells transiently transfected with wild-type (wt) or mutagenized cDNAs (PMID: 19396826), which showed enzyme activity of 4.2 nmol/h/mg cell protein (Wild-type 1005.7 nmol/h/mg cell protein) (PS3_Supporting).

Curation History

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