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Variant: NM_000203.5(IDUA):c.457A>T (p.Lys153Ter)

Version: 1.0

CA355961530

917689 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2ec25cc1-c5c3-48be-82e7-60691c3683c9
Approved on: 2025/4/21
Published on: 2025/5/2

HGVS expressions

NM_000203.5:c.457A>T
NM_000203.5(IDUA):c.457A>T (p.Lys153Ter)
NC_000004.12:g.1000953A>T
CM000666.2:g.1000953A>T
NC_000004.11:g.994741A>T
CM000666.1:g.994741A>T
NC_000004.10:g.984741A>T
NG_008103.1:g.18957A>T
ENST00000247933.9:c.457A>T
ENST00000514224.2:c.457A>T
ENST00000652070.1:n.513A>T
ENST00000247933.8:c.457A>T
ENST00000502910.5:c.316A>T
ENST00000504568.5:c.417A>T
ENST00000506561.5:n.466A>T
ENST00000508168.5:n.335A>T
ENST00000509948.5:c.250A>T
ENST00000514192.5:c.274A>T
ENST00000514224.1:c.61A>T
ENST00000514698.5:n.357A>T
NM_000203.4:c.457A>T
NR_110313.1:n.545A>T
NM_001363576.1:c.61A>T

Pathogenic

Met criteria codes 3

PVS1 PM2_Supporting PM3

Not Met criteria codes 1

PP4

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.457A>T (p.Lys153Ter) in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 4 out of 14, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). Furthermore, SpliceAI predicts that the variant may impact splicing (score for loss of intron 3 acceptor = 0.55; score for loss of intron 4 donor = 0.42). Three individuals reported in the MPS I registry are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen LD VCEP, two with a reported severe phenotype with c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908), and one with an attenuated phenotype with c.1598C>G (p.Pro533Arg) (ClinVar Variation ID: 11910). The phase is unknown is all three cases (PM3, based on 3 x 0.5 points). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00003332 (2/60024 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). In summary, this variant meets the criteria to be classified as pathogenic for mucopolysaccharidosis type I. IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen LD VCEP (Specifications Version 1.0.0.): PVS1, PM3, PM2_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 21, 2025).

Met criteria codes

PVS1	✔	The NM_000203.5:c.457A>T (p.Lys153Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 4 out of 14, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). Furthermore, SpliceAI predicts that the variant may impact splicing (score for loss of intron 3 acceptor = 0.55; score for loss of intron 4 donor = 0.42).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00003332 (2/60024 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).
PM3	✔	Three individuals reported in the MPS I registry are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen LD VCEP, two with a reported severe phenotype with c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908), and one with an attenuated phenotype with c.1598C>G (p.Pro533Arg) (ClinVar Variation ID: 11910). The phase is unknown is all 3 cases. 3 X 0.5 = 1.5 points (PM3).

Not Met criteria codes

PP4	✖	3 individuals with the variant are reported in the MPS I registry, 2 with a severe phenotype and one with an attenuated phenotype. Insufficient data to apply PP4 (PMID: 31194252).

Curation History



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