Variant: NM_000203.5(IDUA):c.1205G>A (p.Trp402Ter)

Version: 1.0

CA220498

11908 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4bf1080d-3923-4e5d-bbb9-af264a5bb56f
Approved on: 2025-01-03
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HGVS expressions

NM_000203.5:c.1205G>A
NM_000203.5(IDUA):c.1205G>A (p.Trp402Ter)
NC_000004.12:g.1002747G>A
CM000666.2:g.1002747G>A
NC_000004.11:g.996535G>A
CM000666.1:g.996535G>A
NC_000004.10:g.986535G>A
NG_008103.1:g.20751G>A
ENST00000247933.9:c.1205G>A
ENST00000514224.2:c.1205G>A
ENST00000652070.1:n.1261G>A
ENST00000247933.8:c.1205G>A
ENST00000502829.1:n.7G>A
ENST00000514224.1:c.809G>A
ENST00000514698.5:n.1312G>A
NM_000203.4:c.1205G>A
NR_110313.1:n.1293G>A
NM_001363576.1:c.809G>A

Pathogenic

Met criteria codes 3
PM3 PVS1 PP4

Not Met criteria codes 3
PM2 BS1 PS3

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.1205G>A (p.Trp402Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 9 out of a total of 14 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. Complete loss of IDUA activity was confirmed when the variant was transiently expressed in COS-7 cells (PMID: 11735025) (PVS1). This is the most common variant to be identified in patients with mucopolysaccharidosis type 1 (MPS1) in the United States (45% of alleles), Mexico (29%), Colombia (50%), Brazil (29%), the United Kingdom (45%), the Netherlands (42%), Germany (50%), the Czech Republic and Slovakia (33%), Spain (62%) and Australia (34%) (reviewed in PMID: 29393969). At least 38 homozygotes (PMID: 1301196, 28752568) (max PM3 points = 2 x 0.5 = 1 point for homozygotes), and at least 73 individuals who are compound heterozygous for the variant and a second variant in IDUA, including another well-known pathogenic variant, p.Gln70Ter, have been reported (PMID: 1301941, 11735025, 28752568, 30809705). The allelic evidence from these compound heterozygous patients will be used to support the classification of the other variant and is not included here to avoid circular logic (PM3 based on evidence from homozygotes). Patients are reported with detailed clinical features of MPS I or elevated urine GAGs in addition to documentation of laboratory values showing deficient IDUA activity (PMID: 1301941, 11735025, 30809705) (PP4). A knock in mouse, homozygous for a variant analogous to p.Trp402Ter (mouse Idua Trp392Ter) was reported to have a phenotype that closely correlates with features in humans patients with MPS1 (PMID: 19751987). The highest population minor allele frequency in gnomAD v4.1.0 is 0.001555 (1749/1124730 alleles) in the European non-Finnish population, which is higher than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025) and lower than the threshold for BS1 (>0.0025). Therefore, no population codes are met. Additional data is available in the literature but the classification of pathogenic has already been reached. There is a ClinVar entry for this variant (Variation ID: 11908). In summary, this variant is the most frequently reported variant in individuals with MPS1 and meets the criteria to be classified as pathogenic for this disorder. IDUA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases VCEP (Specifications Version 1.0.0): PVS1, PM3, PP4. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on January 3, 2025)

Met criteria codes

PM3	✔	At least 38 homozygotes (max 1 point) (PMID: 1301196, 28752568), and at least 73 individuals who are compound heterozygous for the variant and a second variant in IDUA, including another well-known pathogenic variant, p.Gln70Ter, have been reported (max 1 point) (PMID: 1301941, 11735025, 28752568, 30809705) (PM3). The allelic data for many of these patients will be used in the classification of the second variant and is not included here to avoid circular logic.
PVS1	✔	The NM_000203.5:c.1205G>A (p.Trp402Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 9 out of a total of 14 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. When transiently expressed in COS cells, the variant resulted in complete loss of IDUA activity (PMID: 11735025) (PVS1).
PP4	✔	Patients are reported with clinical features of MPS1 and/or elevated urine GAGs in addition to documentation of laboratory values showing deficient IDUA activity (PMID: 1301941, 11735025, 30809705) (PP4).

Not Met criteria codes

PM2	✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.001555 (1749/1124730 alleles) in the European non-Finnish population, which is higher than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025). Therefore, this criterion is not met.
BS1	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.001418 (69/48650 alleles) in the European non-Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for BS1 (>0.0025). Therefore, this criterion is not met.

PS3	✖	Data recorded under PVS1, per SVI guidance for loss of function variants.

Curation History