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# *Variant: NM_000203.5(IDUA):c.1163C>A (p.Thr388Lys)*

Version: 1.0

*CA247499*

*198696 (ClinVar)*

**Gene**: IDUA (HGNC:3425)
**Condition**: mucopolysaccharidosis type 1 (MONDO:0001586)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 748dede1-7d86-40ee-ac1f-025f33b5cbf3
**Approved on**: 2025/8/8
**Published on**: 2025/12/5

## *HGVS expressions*

**NM_000203.5(IDUA):c.1163C>A (p.Thr388Lys)**
**NM_000203.5:c.1163C>A**
NC_000004.12:g.1002459C>A
CM000666.2:g.1002459C>A
NC_000004.11:g.996247C>A
CM000666.1:g.996247C>A
NC_000004.10:g.986247C>A
NG_008103.1:g.20463C>A
ENST00000247933.9:c.1163C>A
ENST00000514224.2:c.1163C>A
ENST00000652070.1:n.1219C>A
ENST00000247933.8:c.1163C>A
ENST00000514224.1:c.767C>A
ENST00000514698.5:n.1270C>A
NM_000203.4:c.1163C>A
NR_110313.1:n.1251C>A
NM_001363576.1:c.767C>A

**Likely Pathogenic**

**Met criteria codes** 5

PM2_Supporting | PP3 | PP4_Moderate | PM5_Supporting | PM3_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.1163C>A variant in IDUA is a missense variant predicted to cause substitution of threonine by lysine at amino acid 388 (p.Thr388Lys). This variant was detected in one homozygous patient with MPS I (PM3 _Supporting). This patient presented with clinical symptoms consistent with MPS I, as well as reduced IDUA activity in leukocytes and elevated total GAGs in urine (PP4_Moderate). The computational predictor REVEL gives a score of 0.756 (PP3). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000244 (1/40992 alleles) in the East Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 198696). 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 Diseases Variant Curation Expert panel (Specifications Version 1.0.0): PP4_Moderate, PP3, PM2_Supporting, PM3_Supporting, PM5_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on August 8, 2025)**

**Met criteria codes**

| | | |
|---|---|---|
| **PM2_Supporting** | ✔ | The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000244 (1/40992 alleles) in the East Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). |
| **PP3** | ✔ | The computational predictor REVEL gives a score of 0.756 which is in the range 0.644-0.773, evidence that correlates with impact to IDUA function at the supporting level (PMID: 36413997) (PP3). |
| **PP4_Moderate** | ✔ | At least 1 patient with this variant had documented IDUA deficiency within the affected range in leukocytes ( 2 points), and urinary GAGs expressed as total GAGs above normal range (1 point), and clinical features specific to MPS I including hepatosplenomegaly, arthropathy, corneal involvement, valvular thickening (1 point). (4 points total, PMID: 27520059, PP4_Moderate). |
| **PM5_Supporting** | ✔ | Another variant at the same amino acid position, c.1163C>G (pThr388Arg) has been classified as likely pathogenic by the ClinGen LD VCEP (PM5_Supporting). |
| **PM3_Supporting** | ✔ | This variant has been detected in at least 1 individual with MPS I. That individual was homozygous for the variant (0.5 points, PMID: 27520059) (PM3_Supporting) |

Curation History

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