# *Variant: NM_000203.5(IDUA):c.614G>A (p.Cys205Tyr)*

Version: 1.0

*CA355961928*

*1468875 (ClinVar)*

**Gene**: IDUA (HGNC:3425)
**Condition**: mucopolysaccharidosis type 1 (MONDO:0001586)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** cb14f5c1-0161-4c8a-9130-0c8fdabcef15
**Approved on**: 2024-12-06
**Published on**: 2025-06-07

## *HGVS expressions*

**NM_000203.5:c.614G>A**
NM_000203.5(IDUA):c.614G>A (p.Cys205Tyr)
NC_000004.12:g.1001703G>A
CM000666.2:g.1001703G>A
NC_000004.11:g.995491G>A
CM000666.1:g.995491G>A
NC_000004.10:g.985491G>A
NG_008103.1:g.19707G>A
ENST00000247933.9:c.614G>A
ENST00000514224.2:c.614G>A
ENST00000652070.1:n.670G>A
ENST00000247933.8:c.614G>A
ENST00000502910.5:c.473G>A
ENST00000504568.5:c.574G>A
ENST00000509948.5:c.407G>A
ENST00000514192.5:c.431G>A
ENST00000514224.1:c.218G>A
ENST00000514698.5:n.514G>A
NM_000203.4:c.614G>A
NR_110313.1:n.702G>A
NM_001363576.1:c.218G>A

**Likely Pathogenic**

**Met criteria codes** 5

PP4 PP3_Moderate PM2_Supporting PS3_Supporting PM3_Supporting

**Not Met criteria codes** 2

PS1 PM5

Evidence Links 0

## Expert Panel

Lysosomal Diseases VCEP

## Criteria Specification Information

**Criteria Specification:** *ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
**Criteria Specification Approval History**
**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Lysosomal Diseases VCEP***

**The NM_000203.5:c.614G>A variant in IDUA is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 205 (p.Cys205Tyr). Two patients with a diagnosis of MPS I are reported to be compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic or likely pathogenic for MPS I by the ClinGen LD VCEP. The phase is unconfirmed in both cases. The second variant is c.501C>A (p.Tyr167Ter) in one patient (pathogenic, 0.5 points, PMID: 11735025) and c.1240delA in the second patient (likely pathogenic, PMID: 28752568, 0.25 points). Total points = 0.75 (PM3_Supporting). One of these individuals was described as having symptoms typical of attenuated MPS I (Scheie syndrome) with documentation of low IDUA activity values (PMID: 11735025) (PP4). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002202 (2/90842 alleles) in the South Asian population which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). Expression of the variant in COS-7 resulted in <1% wild-type IDUA activity indicating that this variant may impact protein function (Table 8, PMID: 11735025) (PS3_Supporting). The computational predictor REVEL gives a score of 0.951, 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). Three other missense variants have been reported at the same amino acid position: c.613T>G (p.Cys205Gly) (ClinVar Variation ID: 2184620, LP in ClinVar), c.613T>A (p.Cys205Ser) (ClinVar Variation ID: 2145829, VUS in ClinVar), and c.615C>G (p.Cys205Trp) (ClinVar Variation ID: 3613351, LP in ClinVar). The classification of the current variant, c.614G>A (p.Cys205Tyr), will be used in the assessment of the other variants at Cys205. Therefore, PM5 is not applied in order to avoid circular logic. In summary, this variant meets the criteria to be classified as likely pathogenic for MPS I. IDUA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP (Specifications Version 1.0.0): PP3_Moderate, PP4, PS3_Supporting. PM3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 6, 2024)**

**Met criteria codes**

| | | |
|---|---|---|
| **PP4** | ✔ | Two patients with this variant have been reported. One was described as having symptoms typical of attenuated MPS I (Scheie syndrome) with documentation of low IDUA activity values (PMID: 11735025) (PP4). |
| **PP3_Moderate** | ✔ | The computational predictor REVEL gives a score of 0.951, 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). |
| **PM2_Supporting** | ✔ | The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002202 (2/90842 alleles) in the South Asian population which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). |
| **PS3_Supporting** | ✔ | Expression of the variant in COS-7 resulted in <1% wild-type IDUA activity indicating that this variant may impact protein function (Table 8, PMID: 11735025) (PS3_Supporting). |
| **PM3_Supporting** | ✔ | Two patients with a diagnosis of MPS I are reported to be compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic or likely pathogenic for MPS I by the ClinGen LD VCEP. The phase is unconfirmed in both cases. The second variant is c.501C>A (p.Tyr167Ter) in one patient (pathogenic, 0.5 points, PMID: 11735025) and c.1240delA in the second patient (likely pathogenic, PMID: 28752568, 0.25 points). Total points = 0.75 (PM3_Supporting). |

**Not Met criteria codes**

| | | | |
|---|---|---|---|
| **PS1** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PM5** | | ✖ | Three other missense variants have been reported at the same amino acid position: c.613T>G (p.Cys205Gly) (ClinVar Variation ID: 2184620, LP in ClinVar), c.613T>A (p.Cys205Ser) (ClinVar Variation ID: 2145829, VUS in ClinVar), and c.615C>G (p.Cys205Trp) (ClinVar Variation ID: 3613351, LP in ClinVar). The classification of the current variant, c.614G>A (p.Cys205Tyr), will be used in the assessment of the other variants at Cys205. Therefore, PM5 is not applied in order to avoid circular logic. |

Curation History

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