

Variant: *NM_001363576.1:c.430G>A*

Version: 1.0

CA355962355 [↗](#)

3233261 (ClinVar) [↗](#)

Gene: IDUA ([HGNC:3425](#))

Condition: mucopolysaccharidosis type 1 ([MONDO:0001586](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 4d0d306d-ad40-4e0f-8278-e402d15ad508

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HGVS expressions

NM_001363576.1:c.430G>A

NC_000004.12:g.1002015G>A

CM000666.2:g.1002015G>A

NC_000004.11:g.995803G>A

CM000666.1:g.995803G>A

NC_000004.10:g.985803G>A

NG_008103.1:g.20019G>A

ENST00000247933.9:c.826G>A

ENST00000514224.2:c.826G>A

ENST00000652070.1:n.882G>A

ENST00000247933.8:c.826G>A

ENST00000514192.5:c.643G>A

ENST00000514224.1:c.430G>A

ENST00000514698.5:n.826G>A

NM_000203.4:c.826G>A

NR_110313.1:n.914G>A

NM_000203.5:c.826G>A

Likely Pathogenic

Met criteria codes 5

PS3_Supporting

PP3_Moderate

PP4

PM3

PM2_Supporting

Not Met criteria codes 11

BP5

BP7

BP3

BP2

BS4

PP1

PM6

PM1

PM5

PS1

PS2

Evidence Links 1

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.826G>A in IDUA is a missense variant resulting in the substitution of glutamate by lysine at amino acid 276 (p.Glu276Lys). This variant has been reported in at least five probands with MPS I, all with a milder phenotype. In one patient homozygous for this genetic change (PMID 21364962), a highly-specific combination of clinical and biochemical evidence for MPS I has been reported (PMID: 21364962) (PP4). All other probands are also reported to have a confirmed enzymatic diagnosis. This variant has been detected in at least five probands with MPS I in the available literature. There is at least one homozygous patient of Thai ancestry (PMID 21364962), and three Turkish siblings (reported in PMID 23786846, but potentially the same proband as in PMID 21394825), scoring 1 point in total (max for homozygous individuals). Two individuals are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic or likely pathogenic for MPS I including c.208C>T (p.Gln70Ter) (ClinVar Variation ID: 11909) (P by LD VCEP, phase unconfirmed, 0.5 points) (PMID: 35141277), and c.494-1G>A (ClinVar Variation ID: 557942) (LP by LD VCEP, phase unconfirmed, 0.25 points) (PMID: 21394825). Another individual is compound heterozygous for the variant and c.250G>C (p.Gly84Arg). The allelic data from the latter patient will be used in the classification of p.Gly84Arg and is not included here to avoid circular logic. Total 1.75 points (PM3). Experimental evidence from a COS-7 cell line, with c.826G>A expressed through site-directed mutagenesis, demonstrated minimal residual enzyme activity (approximately 1%) (PMID 21364962) (PS3_Supporting). The computational predictor REVEL gives a score of 0.833 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). The highest population minor allele frequency in gnomAD v4.1.0. is 8.522e-7 (1/1173452 alleles) in the European (non-Finnish) 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 likely pathogenic for MPS I. IDUA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 1.0.0.): PM3, PP3_Moderate, PP4, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 23, 2025).

Met criteria codes

PS3_Supporting			Prommajan et al. (2011) transiently transfected the c.826G>A variant into COS-7 cells. The experiment was performed twice in triplicate, included a positive and negative control and accounted for the background IDUA activity in COS-7 cells, though there was no evidence that sequencing was used to confirm that the engineered mutation was present in the COS-7 cells after site-directed mutagenesis. Once the background enzyme activity is subtracted out, the residual enzyme activity is around 1%. Overall this appears to meet criteria in itself to apply PS3_Supporting.
			Prommajan et al. (2011) transiently transfected the c.826G>A variant into COS-7 cells. The experiment was performed twice in triplicate, included a positive and negative control and accounted for the background IDUA activity in COS-7 cells, though there was no evidence that sequencing was used to confirm that the engineered mutation was present in the COS-7 cells after site-directed mutagenesis. Once the background enzyme activity is subtracted out, the residual enzyme activity is around 1%. Overall this appears to meet criteria in itself to apply PS3_Supporting. PubMed:21364962 
PP3_Moderate			The computational predictor REVEL gives a score of 0.833 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).
PP4			Patient 2 from PMID 21364962 has two (claw hand deformity i.e. arthropathy and corneal opacity) specific clinical features of MPS (one criterion met). They also have alpha-L-iduronidase enzyme activity that is well outside the normal range (0.61 nmol/h/mg protein; mean and SD in controls of 23.10±8.80 nmol/h/mg protein)(second criterion met). Since two criteria are met, PP4 can be applied at its standard strength.
PM3			This variant has been detected in at least five probands with MPS I in the available literature. There is at least one homozygous patient of Thai ancestry (PMID 21364962), and three Turkish siblings (reported in PMID 23786846, but potentially the same proband as in PMID 21394825), scoring 1 point in total (max for homozygous individuals). Two individuals are compound heterozygous for the variant and another variant in IDUA that has been classified as

pathogenic or likely pathogenic for MPS I including c.208C>T (p.Gln70Ter) (ClinVar Variation ID: 11909) (P by LD VCEP, phase unconfirmed, 0.5 points) (PMID: 35141277), and c.494-1G>A (ClinVar Variation ID: 557942) (LP by LD VCEP, phase unconfirmed, 0.25 points) (PMID: 21394825). Another individual is compound heterozygous for the variant and c.250G>C (p.Gly84Arg). The allelic data from the latter patient will be used in the classification of p.Gly84Arg and is not included here to avoid circular logic. Total 1.75 points (PM3)

PM2_Supporting





The highest population minor allele frequency in gnomAD v4.1.0. is 8.522e-7 (1/1173452 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).

Not Met criteria codes

BP5			There is no known alternate molecular basis for deficiency of alpha-L-iduronidase activity, other than variants in IDUA.
BP7			This is a missense variant: this criterion does not apply.
BP3			This is a missense variant: this criterion does not apply.
BP2			This variant has not been reported to be in cis with a pathogenic variant in any patients with MPS I.
BS4			Lack of familial segregation has not been reported for this variant.
PP1			Co-segregation in multiple affected family members has not been reported for this variant.
PM6			This variant has not been reported as a de novo change.
PM1			This variant does not involve one of the specific residues known to be crucial to the function of IDUA.
PM5			No pathogenic/likely pathogenic missense changes have been reported at this amino acid residue. There are two reports of the missense change c.828G>C causing p.(Glu276Asp), both of which have classified this variant as a variant of uncertain significance.
PS1			No other established pathogenic variants are reported with the same amino acid change.
PS2			This variant has not been reported as a de novo change.

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