

Variant: *NM_000203.5(IDUA):c.544G>A (p.Glu182Lys)*

Version: 1.0

CA2801988 [↗](#)

2198440 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: dab8950c-afd5-4ca1-9060-21d2422d809a

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HGVS expressions

NM_000203.5(IDUA):c.544G>A (p.Glu182Lys)

NM_000203.5:c.544G>A

NC_000004.12:g.1001518G>A

CM000666.2:g.1001518G>A

NC_000004.11:g.995306G>A

CM000666.1:g.995306G>A

NC_000004.10:g.985306G>A

NG_008103.1:g.19522G>A

ENST00000247933.9:c.544G>A

ENST00000514224.2:c.544G>A

ENST00000652070.1:n.600G>A

ENST00000247933.8:c.544G>A

ENST00000502910.5:c.403G>A

ENST00000504568.5:c.504G>A

ENST00000509948.5:c.337G>A

ENST00000514192.5:c.361G>A

ENST00000514224.1:c.148G>A

ENST00000514698.5:n.444G>A

NM_000203.4:c.544G>A

NR_110313.1:n.632G>A

NM_001363576.1:c.148G>A

Pathogenic

Met criteria codes 5

PS3_Supporting

PM3_Supporting

PP3_Moderate

PM1

PM2_Supporting

Not Met criteria codes 2

PP4

PM5

Evidence Links 2

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**

The NM_000203.5:c.544G>A variant in IDUA is predicted to result in the missense substitution of glutamine by lysine at amino acid 182 (p.Glu182Lys). This residue, Glu182 is one of the active site residues of IDUA; a role that has been shown by multiple homology modeling, crystallography, and functional studies (PMID: 11555618, 15862278, 23959878, 24036510, 24480078). Two patients with MPS 1 have been reported with the variant but there is insufficient evidence to apply PP4. One of these patients, with severe MPS 1 is compound heterozygous for the variant and a variant in IDUA that has been classified as pathogenic by the ClinGen LD VCEP, c.1205G>A (p.Trp402Ter) (ClinGen Variation ID: 11908). The phase is unknown (PMID: 11555618, 12559846). Another patient, with attenuated symptoms, is compound heterozygous for the variant and c.712T>A (p.Leu238Gln); The allelic data for this patient will be used in the assessment of p.Leu238Gln and is not included here to avoid circular logic. (PM3_Supporting). As noted, Glu182 has been shown to be important in the active site of IDUA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (PMID: 23959878, 24036510, 24480078) (PM1). When expressed in CHO cells and HAP1 cells , the variant resulted in no IDUA activity across multiple studies (PMID: 11555618, 12559846, 33198351) (PS3_Supporting). The computational predictor REVEL gives a score of 0.928 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 8.475e-7 (1/1179960 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). Other missense substitutions at the same amino acid have been reported in affected individuals, including c.546G>C (p.Glu182Asp) (PMID: 21480867), and c.544G>C (p.Glu182Gln) (homozygous individual reported in the Iran Variome MPS Database, <https://variome.ir/lovd/genes/IDUA>). The LD VCEP has not yet classified these variants and therefore, this data will not be used to support the classification of c.544G>A (p.Glu182Lys). There is a ClinVar entry for this variant (Variation ID: 2198440). The classification has been modified from likely pathogenic to pathogenic based on extensive evidence showing that Glu182 is an active site residue, with multiple functional, crystallography, and modeling studies (stacking evidence). In summary, these variant meets the criteria to be classified as pathogenic for mucopolysaccharidosis type 1. IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 1.0.0): PM1, PP3_Moderate, PS3_Supporting, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 6, 2024)

Met criteria codes

PS3_Supporting			When expressed in CHO cells and HAP1 cells , the variant resulted in no IDUA activity across multiple studies (PMID: 11555618, 12559846, 33198351) (PS3_Supporting).
			Site-directed mutagenesis of a wild-type pEF-IDUA vector, followed by sequencing to confirm the presence of the variant, and absence of other sequence changes. CHO-K1 cells were transfected with wild type or variant IDUA cDNA. Transfected cells were selected (using G418), followed by culture of 3 lines per variant. When expressed in CHO-K1 cells, no specific IDUA activity was detected for variant p.Glu182Lys (Table 4) (PMID: 12559846) PubMed:12559846  After viral delivery of IDUA cDNA containing the variant into IDUA-deficient HAP1 cells and isolation of single cell expression clones, enzyme activity was measured for two clones (p.Glu182Lys-C5, p.Glu182Lys-D1) and was extremely low (0.0076 and 0.0003% of WT for activity/total protein; and 0.031% and 0.001% WT activity/enzyme abundance respectively). The authors describe the variant as “catalytically dead” and use is as a control for an variant that obliterates the activity. PubMed:33198351 
PM3_Supporting			One patient with MPS 1 have been reported to be compound heterozygous for the variant and a variant in IDUA that has been classified as pathogenic by the ClinGen LD VCEP, c.1205G>A (p.Trp402Ter) (ClinGen Variation ID: 11908). The phase is unknown (PMID: 11555618, 12559846) (0.5 points). Another patient is compound heterozygous for the variant and c.712T>A (p.Leu238Gln); The allelic data for this patient will be used in the assessment of p.Leu238Gln and is not included here to avoid circular logic.
PP3_Moderate			The computational predictor REVEL gives a score of 0.928 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).

PM1

This variant alters amino acid Glu182, a residue that has been shown to be important in the active site of IDUA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (PMID: 23959878, 24036510, 24480078) (PM1).

PM2_Supporting

The highest population minor allele frequency in gnomAD v4.1.0 is 8.475e-7 (1/1179960 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

PP4

Two patients with MPS 1 have been reported with the variant but there is insufficient evidence to apply PP4.

PM5

Other missense substitutions at the same amino acid have been reported in affected individuals, including c.546G>C (p.Glu182Asp) (PMID: 21480867), and c.544G>C (p.Glu182Gln) (homozygous individual reported in the Iran Variome MPS Database, <https://variome.ir/lovd/genes/IDUA>). The LD VCEP has not yet classified these variants and therefore, this data will not be used to support the classification of c.544G>A (p.Glu182Lys).

Curation History [↗](#)

Showing 1 to 1 of 1 rows

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