

Variant: *NM_000203.5(IDUA):c.623G>A (p.Gly208Asp)*

Version: 1.0

CA355961948 [↗](#)

554590 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 44be170b-ab83-4d06-a4a7-18228a674ea7

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HGVS expressions

NM_000203.5:c.623G>A

NM_000203.5(IDUA):c.623G>A (p.Gly208Asp)

NC_000004.12:g.1001712G>A

CM000666.2:g.1001712G>A

NC_000004.11:g.995500G>A

CM000666.1:g.995500G>A

NC_000004.10:g.985500G>A

NG_008103.1:g.19716G>A

ENST00000247933.9:c.623G>A

ENST00000514224.2:c.623G>A

ENST00000652070.1:n.679G>A

ENST00000247933.8:c.623G>A

ENST00000502910.5:c.482G>A

ENST00000504568.5:c.583G>A

ENST00000509948.5:c.416G>A

ENST00000514192.5:c.440G>A

ENST00000514224.1:c.227G>A

ENST00000514698.5:n.523G>A

NM_000203.4:c.623G>A

NR_110313.1:n.711G>A

NM_001363576.1:c.227G>A

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP4_Moderate

PP3_Moderate

PS3_Moderate

PM3_Strong

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**

Lysosomal Diseases VCEP

The NM_000203.5:c.623G>A variant in IDUA is a missense variant in exon 6, where glycine at amino acid position 208 is replaced with an aspartic acid (p.Gly208Asp). This variant has been reported in at least seven probands with MPS I (PMID: 21480867, 29976218, 26446585, 24480078). At least 5 probands are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP including c.208C>T (p.Gln70Ter) (ClinVar Variation ID: 11909) (PMID: 12509712, 24480078) (confirmed in trans by parental testing, 1 point), c.1598C>G (p.Pro533Arg) (ClinVar Variation ID: 11910) (PMID: 29976218; 2 patients who may be sibs, unconfirmed phase; 0.5 points), c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (PMID: 12559846; phase unconfirmed, 0.5 points), and c.657dupG (typo as there is no G in the reference sequence at this position; therefore data not included) (PMID: 21480867). There is also one patient who is homozygous for the variant (PMID: 29976218) (0.5 points) (total 2.5 points; PM3_Strong). Another patient is compound heterozygous for the variant and a variant reported by the authors as p.Pro520Arg (PMID: 26446585). The amino acid Proline at location 520 was not found in any reference sequence for IDUA. One patient with the variant is a 10-month-old male with a Hurler phenotype, with IDUA activity leukocytes of 1.5 nmol/h/mg protein (Normal range in Chinese controls: 27.2-52 nmol/h/mg protein). The proband exhibits delayed mental development, macrocephaly, joint stiffness, Mongolian macula, hepatosplenomegaly, hernia, cardiac disease, and airway obstruction (PMID: 21480867) (PP4_Moderate). The highest population minor allele frequency in gnomAD v4.1.0 is 0.000013 (1/74860 alleles) in the African/African American population , which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). Expressing the mutation in CHO-K1 cells resulted in 0.0006% normal alpha-iduronidase activity compared to the wild-type control, as shown by western blots (PMID: 12559846). Western blots show no full-length protein (PS3_Moderate). The computational predictor REVEL yields a score of 0.959, which exceeds the threshold of 0.773, indicating a correlation with the impact on IDUA function, as specified in the ClinGen Lysosomal Diseases VCEP (PMID: 36413997) (PP3_Moderate). There is a ClinVar entry for this variant (ClinVar variation ID: 554590). In summary, this variant meets the criteria to be classified as 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): PM3_Strong, PP3_Moderate, PP4_Moderate, PS3_Moderate, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, Sept. 15, 2025)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0 in the African population is 0.000013 (1/74860), which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.00025), due to which we can apply PM2_Supporting.
PP4_Moderate			A 10-month-old male with a hurler phenotype, compound heterozygous with c.623 G>A and c.657dupG mutation. Has IDUA activity leukocytes of 1.5 nmol/h/mg protein (Normal range in Chinese controls: 27.2-52 nmol/h/mg protein). The proband exhibits delayed mental development, macrocephaly, joint stiffness, Mongolian macula, hepatosplenomegaly, hernia, cardiac disease, and airway obstruction (PMID: 21480867) (PP4_Moderate)
PP3_Moderate			The computational predictor REVEL yields a score of 0.959, which exceeds the threshold of 0.773, indicating a correlation with the impact on IDUA function, as specified in the ClinGen Lysosomal Diseases VCEP (PMID: 36413997) (PP3_Moderate)
PS3_Moderate			Expressing the mutation in CHO-K1 cells led to 0.0006% normal alpha-iduronidase activity compared to the wildtype control - western blots provided (PMID: 12559846) PS3_Moderate.
PM3_Strong			At least 5 probands are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP including c.208C>T (p.Gln70Ter) (ClinVar Variation ID: 11909) (PMID: 12509712, 24480078) (confirmed in trans by parental testing, 1 point), c.1598C>G (p.Pro533Arg) (ClinVar Variation ID: 11910) (PMID: 29976218; 2 patients who may be sibs, unconfirmed phase; 0.5 points), c.1205G>A

(p.Trp402Ter) (ClinVar Variation ID: 11908) (PMID: 12559846; phase unconfirmed, 0.5 points), and c.657dupG (typo as there is no G in the reference sequence at this position) (PMID: 21480867). One patient who is homozygous for the variant (PMID: 29976218) (0.5 points) (total 2.5 points; PM3_Strong).

Curation History [↗](#)

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