The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000203.5(IDUA):c.1045_1047del (p.Asp349del)

Version: 1.0

CA438057772

557885 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: b614762f-5166-4d98-9285-ed017b846e39
Approved on: 2025/4/7
Published on: 2025/4/7

HGVS expressions

NM_000203.5(IDUA):c.1045_1047del (p.Asp349del)
NM_000203.5:c.1045_1047del
NC_000004.12:g.1002341_1002343del
CM000666.2:g.1002341_1002343del
NC_000004.11:g.996129_996131del
CM000666.1:g.996129_996131del
NC_000004.10:g.986129_986131del
NG_008103.1:g.20345_20347del
ENST00000247933.9:c.1045_1047del
ENST00000514224.2:c.1045_1047del
ENST00000652070.1:n.1101_1103del
ENST00000247933.8:c.1045_1047del
ENST00000514224.1:c.649_651del
ENST00000514698.5:n.1152_1154del
NM_000203.4:c.1045_1047del
NR_110313.1:n.1133_1135del
NM_001363576.1:c.649_651del

Pathogenic

Met criteria codes 6

PM4_Supporting PM3_Strong PM2_Supporting PM1 PP3 PP4

Not Met criteria codes 3

PM5 PS1 PS3

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5(IDUA):c.1045_1047del (p.Asp349del) variant in IDUA is predicted to cause a change in the length of the protein due to an in-frame deletion of 1 amino acid in a non-repeat region (p.Asp349del) (PM4_Supporting). This variant removes amino acid Asp349, a residue that has been shown to be important in substrate binding in IDUA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (PMID: 23959878, 24036510) (PM1). At least 4 probands have been reported with the variant, all with a diagnosis of MPS I and including patients with very low IDUA activity, and elevated urine GAGs (PMID: 36837830) or detailed clinical symptoms consistent with the condition (PMID: 27351199) (PP4). Of those individuals, 2 were compound heterozygous, phase unknown, for the variant and a variant that has been classified as pathogenic by the ClinGen LD VCEP; either c.713T>A (p.Leu238Gln) (PMID: 27351199, 0.5 points) or c.208C>T (p.Gln70Ter) (PMID: 21394825, 27392569, 0.5 points; cannot confirm that these reports are not the same patient). Two patients are homozygous for the variant (PMID: 21394825, 36837830, 2 x 0.5 points). Total 2 points (PM3_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002229 (1/44872 alleles) in the East Asian population (PM2_Supporting). In silico predictors suggest that the variant impacts the function of the gene product; Mutation Taster predicts that the variant is "disease-causing", score for MutPredIndel is 0.789 (>0.5 for deleterious) (PP3). There is a ClinVar entry for this variant (Variation ID: 557885). In summary, this variant meets the criteria to be classified as pathogenic for MPS I based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert panel (Specifications Version 1.0.0): PM3_Strong, PM1, PP3, PM2_Supporting, PM4_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 7, 2025).

Met criteria codes

PM4_Supporting	✔	The NM_000203.5:c.1045_1047del variant is predicted to cause a change in the length of the protein (p.Asp349) due to an in-frame deletion of 1 amino acid in a non-repeat region (PM4_supporting).
PM3_Strong	✔	This variant has been detected in at least 4 probands with MPS I. Of those individuals, 2 were compound heterozygous, phase unknown, for the variant and a variant that has been classified as pathogenic by the ClinGen LD VCEP; either c.713T>A (p.Leu238Gln) (PMID: 27351199, 0.5 points) or c.208C>T (p.Gln70Ter) (PMID: 21394825, 27392569, 0.5 points; cannot confirm that these reports are not the same patient). Two patients are homozygous for the variant (PMID: 21394825, 36837830, 2 x 0.5 points). Total 2 points (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002229 (1/44872 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).
PM1	✔	This variant removes amino acid Asp349, a residue that has been shown to be important in substrate binding in IDUA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (PMID: 23959878, 24036510) (PM1).
PP3	✔	In silico predictors suggest that the variant impacts the function of the gene product; Mutation Taster predicts that the variant is "disease-causing", score for MutPredIndel is 0.789 (>0.5 for deleterious) (PP3).
PP4	✔	At least 4 probands have been reported with the variant, all with a diagnosis of MPS I and including patients with very low IDUA activity, and elevated urine GAGs (PMID: 36837830) or detailed clinical symptoms consistent with the condition (PMID: 27351199) (PP4).

Not Met criteria codes

PM5	✖	Not a missense change

PS1		✖	No variants with same amino acid change
PS3		✖	No functional study available

Curation History

howing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.