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Variant: NM_000203.5(IDUA):c.1045G>C (p.Asp349His)

Version: 1.0

CA355963148

2585078 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: a349907c-ea75-4f49-95c7-82ed3e29d8a2
Approved on: 2025/12/21
Published on: 2025/12/29

HGVS expressions

NM_000203.5(IDUA):c.1045G>C (p.Asp349His)
NM_000203.5:c.1045G>C
NC_000004.12:g.1002341G>C
CM000666.2:g.1002341G>C
NC_000004.11:g.996129G>C
CM000666.1:g.996129G>C
NC_000004.10:g.986129G>C
NG_008103.1:g.20345G>C
ENST00000247933.9:c.1045G>C
ENST00000514224.2:c.1045G>C
ENST00000652070.1:n.1101G>C
ENST00000247933.8:c.1045G>C
ENST00000514224.1:c.649G>C
ENST00000514698.5:n.1152G>C
NM_000203.4:c.1045G>C
NR_110313.1:n.1133G>C
NM_001363576.1:c.649G>C

Likely Pathogenic

Met criteria codes 4

PM1 PP3_Moderate PP4 PM2_Supporting

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 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5:c.1045G>C variant in IDUA is a missense variant in Exon 8, where Aspartic acid (Asp, D) is replaced by Histidine (His, H) at position 349, p.(Asp349His). The variant has been reported in at least one proband with MPS I (PMIDs: 35614200). In ClinVar, a patient is reported with this variant (unknown is homozygous or compound heterozygous with a second variant) and clinical symptoms consistent with MPS I (global developmental delay, coarse facies, flat nasal bridge, hypertrichosis, stiffness in knee joint, hyperpigmentation, descended abdomen with splenomegaly), and elevated glycosaminoglycans (132 mg/mM Creat) (SCV004047898.1) (PP4). The highest population minor allele frequency in gnomAD v4.1.0 is 8.476760114470168e-7 (1/1179696 alleles) in the European (non-Finnish) genetic ancestry group; this is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.927, 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). Asp 349 is a critical active site residue. The residue Asp349 is involved in substrate binding of a positively charged environment that ensures a depressed pKa for the carboxyl group of Glu 299 (PMID:24036510) (PM1). In summary, this variant meets the criteria to be classified as likely pathogenic for MPS1 based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Disease Variant Curation Expert Panel (Specifications Version 1.1.0): PM1, PP3_Moderate, PP4, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Disease Variant Curation Expert Panel on December 21, 2025)

Met criteria codes

PM1	✔	Asp 349 is a critical active site residue. The residue Asp349 is involved in substrate binding of a positively charged environment that ensures a depressed pKa for the carboxyl group of Glu 299. PMID:24036510
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.927, 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	✔	In ClinVar Neuberg Centre For Genomic Medicine, NCGM reports a 1-year-6-month-old female child, 2nd born to 3rd third-degree consanguineous marriage, presented with global developmental delay. progressive hearing loss and dysmorphism. Birth history: FT LSCS, oligohydramnios O/E: coarse facies, flat nasal bridge, hypertrichosis, stiffness in joint present (knee joint), hyperpigmentation, descended abdomen with splenomegaly, Proband walks with support at present Investigation: elevated glycosaminoglycans (132 mg/mM Creat) (PP4_Supporting).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 8.476760114470168e-7 (1/1179696 alleles) in the European (non-Finnish) genetic ancestry group; this is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).

Curation History

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