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Variant: NM_000203.5(IDUA):c.1046A>G (p.Asp349Gly)

Version: 1.0

CA2802173

950889 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 669b6e4a-b1bd-4e53-a4ae-823ca1eee427
Approved on: 2024/12/6
Published on: 2025/6/8

HGVS expressions

NM_000203.5(IDUA):c.1046A>G (p.Asp349Gly)
NM_000203.5:c.1046A>G
NC_000004.12:g.1002342A>G
CM000666.2:g.1002342A>G
NC_000004.11:g.996130A>G
CM000666.1:g.996130A>G
NC_000004.10:g.986130A>G
NG_008103.1:g.20346A>G
ENST00000247933.9:c.1046A>G
ENST00000514224.2:c.1046A>G
ENST00000652070.1:n.1102A>G
ENST00000247933.8:c.1046A>G
ENST00000514224.1:c.650A>G
ENST00000514698.5:n.1153A>G
NM_000203.4:c.1046A>G
NR_110313.1:n.1134A>G
NM_001363576.1:c.650A>G

Likely Pathogenic

Met criteria codes 6

PP3_Moderate PM1 PM3 PP4_Moderate PM2_Supporting PM5_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 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000203.5:c.1046A>G (p.Asp349Gly) variant in IDUA results in missense substitution of aspartate to glycine at amino acid 349. This variant alters 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). Two Vietnamese probands are compound heterozygous for the variant and another variant in IDUA that has been classified as likely pathogenic for MPS I by the ClinGen Lysosomal Diseases VCEP, c.1190-10C>A; for one of those patients, the variants were confirmed to be in trans by parental testing (PMID: 34833038) (1.25 points) (PMID: 34833038). These individuals had deficient IDUA activity, elevated urine heparan and dermatan sulfates, and multiple systems involved with clinical features consistent with MPS I (PP4_Moderate). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00013 (10/7,542 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). The computational predictor REVEL gives a score of 0.899 which is above the threshold of 0.773, evidence that correlates with impact to IDUA function at the moderate level (PMID: 36413997) (PP3_Moderate). Several other amino acid substitutions at the same position have been reported, including c.1045G>A (p.Asp349Asn) (ClinVar Variation ID: 92623), c.1045G>T (p.Asp349Tyr) (ClinVar Variation ID: 638075), and c.1045G>C(p.Asp349His) (ClinVar Variation ID: 2585078). One variant, c.1045G>A (p.Asp349Asn), has been classified as likely pathogenic by the ClinGen Lysosomal Diseases VCEP) (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 950889). In summary, this variant meets the criteria to be classified as likely pathogenic for mucopolysaccharidosis type I. IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 1.0.0): PM1, PM3, PP4_Moderate, PM2_Supporting, PM5_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 6, 2024).

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.899 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 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).
PM3	✔	Two probands are compound heterozygous for the variant and another variant in IDUA that has been classified as likely pathogenic for MPS I by the ClinGen Lysosomal Diseases VCEP, c.1190-10C>A; for one of those patients, the variants were confirmed to be in trans by parental testing (PMID: 34833038) (1.25 points) (PMID: 34833038).
PP4_Moderate	✔	Two Vietnamese patients, heterozygous for this allele, had deficient IDUA activity, elevated urine heparan and dermatan sulfates, and multiple systems involved with clinical features consistent with MPS I (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00013 (10/7,542 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).
PM5_Supporting	✔	Several other amino acid substitutions at the same position have been reported, including c.1045G>A (p.Asp349Asn) (ClinVar Variation ID: 92623), c.1045G>T (p.Asp349Tyr) (ClinVar Variation ID: 638075), and c.1045G>C(p.Asp349His) (ClinVar Variation ID: 2585078). One variant, c.1045G>A (p.Asp349Asn), has been classified as likely pathogenic by the ClinGen Lysosomal Diseases VCEP) (PM5_Supporting).

Curation History



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