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Variant: NM_000203.5(IDUA):c.266G>A (p.Arg89Gln)

Version: 1.2

CA256124

11922 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: e751feb6-b285-4f42-96f5-9f0b027d2d4d
Approved on: 2025/4/7
Published on: 2025/6/9

HGVS expressions

NM_000203.5:c.266G>A
NM_000203.5(IDUA):c.266G>A (p.Arg89Gln)
NC_000004.12:g.987916G>A
CM000666.2:g.987916G>A
NC_000004.11:g.981704G>A
CM000666.1:g.981704G>A
NC_000004.10:g.971704G>A
NG_008103.1:g.5920G>A
NG_033042.1:g.10521C>T
ENST00000247933.9:c.266G>A
ENST00000398516.3:c.*917C>T
ENST00000514224.2:c.266G>A
ENST00000247933.8:c.266G>A
ENST00000361661.6:c.*917C>T
ENST00000398520.6:c.576+3212C>T
ENST00000502910.5:c.158+674G>A
ENST00000504568.5:c.259+5G>A
ENST00000506561.5:n.275G>A
ENST00000508168.5:n.177+674G>A
ENST00000509744.1:n.2G>A
ENST00000514698.5:n.199+674G>A
ENST00000622731.4:c.576+3212C>T
NM_000203.4:c.266G>A
NM_022042.3:c.*917C>T
NM_134425.2:c.576+3212C>T
NM_213613.3:c.*917C>T
NR_110313.1:n.354G>A
NM_022042.4:c.*917C>T
NM_134425.3:c.576+3212C>T
NM_213613.4:c.*917C>T
NM_134425.4:c.576+3212C>T

Pathogenic

Met criteria codes 5

PM3_Strong | PM2_Supporting | PM1 | PP4 | PP3_Moderate

Expert Panel

Lysosomal Diseases VCEP

Not Met criteria codes 3

PM5 PS3 PP1

Evidence Links 2

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.266G>A variant in IDUA is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 89 (p.Arg89Gln). This variant accounts for up to 24% of alleles in Japanese individuals with MPS I (PMID: 8664897). At least 8 probands have been reported with the variant, typically with milder clinical features of MPS I and reduced IDUA activity (PMID: 8213840, 8664897, 2148086) (PP4). Of those individuals, 4 probands and one sibling, were compound heterozygous for the variant and variant that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP. None of those were confirmed in trans. The second variants is c.1205G>A (p.Trp402Ter) (PMID: 8213840, 2 patients, 2 x 0.5) and c.613_617dup (p.Glu207AlafsTer29) (PMID: 8664897, 2 probands, 0.5 x 2). Four individuals are homozygous for the variant (PMIDs: 8664897, 21480867, max 2 x 0.5 points). Total 3 points (PM3_Strong). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001662 (1/6016 alleles) in the Middle Eastern population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). This variant alters amino acid Arg89, a residue that has been shown to be important in the active site pocket and substrate binding in IDUA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (PMID: 14559116;15862278) (PM1). The computational predictor REVEL gives a score of 0.941 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). When expressed in CHO cells, the variant results in <5% WT activity (PMID: 14559116), and reduced amount of protein, and reduced specific activity (PMID: 14559116). Two other variants at the same amino acid position, c.265C>G (p.Arg89Gly) (ClinVar Variation ID: 2843836) and c.265C>T (p.Arg89Trp) (ClinVar Variation ID: 580286), have been reported. The evidence for pathogenicity for p.Arg89Gln will be used in the classification of the other two variants and is not included here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 11922). In summary, this variant meets the criteria to be classified as pathogenic for mucopolysaccharidosis type I based on the IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Expert Panel (Specifications Version 1.0.0): PM3_strong, PM1, PP4, PP3_moderate, PM2_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 7, 2025).

Met criteria codes

PM3_Strong	✔	This variant has been detected in at least 8 probands with MPS I. Of those individuals, 4 were compound heterozygous for the variant and variant that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP. None of those were confirmed in trans. The second variants is c.1205G>A (p.Trp402Ter) (PMID: 8213840, 2 patients, 2 x 0.5) and c.613_617dup (p.Glu207AlafsTer29) (PMID: 8664897, 2 probands, 0.5 x 2). Four individuals are homozygous for the variant (PMIDs: 8664897, 21480867, max 2 x 0.5 points). Total 3 points (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001662 (1/6016 alleles) in the Middle Eastern 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 alters amino acid Arg89, a residue that has been shown to be important in Active site pocket and substrate binding in IDUA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (PMID: 14559116;15862278) (PM1).

PP4	✔	At least 8 probands have been reported with the variant, typically with milder clinical features of MPS I and reduced IDUA activity (PMID: 8213840, 8664897, 2148086) (PP4).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.941 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).

Not Met criteria codes

PM5	✖	Two other variants at the same amino acid position, c.265C>G (p.Arg89Gly) (ClinVar Variation ID: 2843836) and c.265C>T (p.Arg89Trp) (ClinVar Variation ID: 580286), have been reported. The evidence for pathogenicity for p.Arg89Gln will be used in the classification of the other two variants and is not included here to avoid circular logic.
PS3	✖	When expressed in CHO cells, the variant results in <5% WT activity (PMID: 14559116), and reduced amount of protein, and reduced specific activity (PMID: 14559116). Table 5: When expressed in CHO cells, specific IDUA activity (pmol/min/ng cell protein) was 10.7 for the variant and 76.7 for the wild type cDNA. PubMed:8213840 When expressed in CHO cells, the variant results in <5% WT activity (Table 2) PubMed:14559116
PP1	✖	Two siblings with Hurler/Scheie confirmed by enzymatic testing are compound heterozygous for the variant. However, results of parents testing are not available, therefore, PP1 will not be applied here.

Curation History

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