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.223G>A (p.Ala75Thr)

Version: 1.0

CA356994

222993 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4b6e7159-db73-4db8-bb8d-c829d4df8c39
Approved on: 2025/5/4
Published on: 2025/5/4

HGVS expressions

NM_000203.5:c.223G>A
NM_000203.5(IDUA):c.223G>A
NM_000203.5(IDUA):c.223G>A (p.Ala75Thr)
NC_000004.12:g.987873G>A
CM000666.2:g.987873G>A
NC_000004.11:g.981661G>A
CM000666.1:g.981661G>A
NC_000004.10:g.971661G>A
NG_008103.1:g.5877G>A
NG_033042.1:g.10564C>T
ENST00000247933.9:c.223G>A
ENST00000398516.3:c.*960C>T
ENST00000514224.2:c.223G>A
ENST00000247933.8:c.223G>A
ENST00000361661.6:c.*960C>T
ENST00000398520.6:c.576+3255C>T
ENST00000502910.5:c.158+631G>A
ENST00000504568.5:c.221G>A
ENST00000506561.5:n.232G>A
ENST00000508168.5:n.177+631G>A
ENST00000514698.5:n.199+631G>A
ENST00000622731.4:c.576+3255C>T
NM_000203.4:c.223G>A
NM_022042.3:c.*960C>T
NM_134425.2:c.576+3255C>T
NM_213613.3:c.*960C>T
NR_110313.1:n.311G>A
NM_022042.4:c.*960C>T
NM_134425.3:c.576+3255C>T
NM_213613.4:c.*960C>T
NM_134425.4:c.576+3255C>T

Pathogenic

Met criteria codes 5

PM3_Strong PP3_Moderate PP4_Moderate PM2_Supporting

Expert Panel

Lysosomal Diseases VCEP

PS3_Supporting

Not Met criteria codes 11

PP1 PM1 PM5 PM4 PM6 BS2 PS1 PS2 BP3 BP5 BP7

Evidence Links 0

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.223G>A variant in IDUA is a missense variant predicted to cause substitution of alanine by threonine at amino acid 75, p.(Ala75Thr). This variant has been seen in at least 11 unrelated patients. Six of these patients are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic, phase not confirmed: c.208C>T (p.Gln70Ter) (PMID: 28752568, 35141277) (ClinVar Variation ID: 11909; 3 patients; max 2 patients counted, 2 x 0.5), c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (PMID: 28752568, 8019563) (3 patients; max 2 patients counted, 2 x 0.5), and 2 individuals are homozygous for the variant (PMID: 11735025, 27146977). In addition, three individuals are compound heterozygous for the variant and either c.895C>T (PMID: 27146977), c.1898C>T (p.Ser633Leu) (PMID: 16438163) or c.1650+1G>T (PMID: 29843745). The allelic data from these patients will be used in the classification of the second variant and is not included here to avoid circular logic. Total points = 3 points (PM3_Strong). One of these individuals has specific clinical features (dysostosis multiplex, hepatosplenomegaly, corneal clouding and coarse facial features), with undetectable IDUA enzyme activity compared to Thai controls, and elevated urinary dermatan and heparan sulfate excretion (PMID: 16438163). This is sufficient for use of PP4_Moderate. The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001335 (1/74900 alleles) in the African/African American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025). Expression of the variant in COS-1 cells resulted in no residual wild type IDUA activity (once background activity subtracted), indicating that this variant may impact protein function (PMID: 7550232)(PS3_Supporting). The computational predictor REVEL gives a score of 0.803 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). There is a ClinVar entry for this variant (Variation ID: 222993). In summary, this variant meets the criteria to be classified as pathogenic. 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_Supporting, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 4, 2025)

Met criteria codes

PM3_Strong	✔	This variant has been seen in at least 11 unrelated patients. Six of these patients are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic, phase not confirmed: c.208C>T (p.Gln70Ter) (PMID: 28752568, 35141277) (ClinVar Variation ID: 11909; 3 patients; max 2 patients counted, 2 x 0.5), c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (PMID: 28752568, 8019563) (3 patients; max 2 patients counted, 2 x 0.5), and 2 individuals are homozygous for the variant (PMID: 11735025, 27146977). In addition, three individuals are compound heterozygous for the variant and either c.895C>T (PMID: 27146977), c.1898C>T (p.Ser633Leu) (PMID: 16438163) or c.1650+1G>T (PMID: 29843745). The allelic data from these patients will be used in the classification of the second variant and is not included here to avoid circular logic. Total points = 3 points (PM3_Strong).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.803 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_Moderate		✔	One patient is reported at four years of age with MPS I, who has specific clinical features (dysostosis multiplex, hepatosplenomegaly, corneal clouding and coarse facial features), with undetectable IDUA enzyme activity compared to Thai controls, and elevated urinary dermatan and heparan sulfate excretion (PMID: 16438163). This is sufficient for use of PP4_Moderate.
PM2_Supporting		✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001335 (1/74900 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).
PS3_Supporting		✔	Expression of the variant in COS-1 cells resulted in no residual wild type IDUA activity (once background activity subtracted), indicating that this variant may impact protein function (PMID: 7550232)(PS3_Supporting).

Not Met criteria codes

PP1		✖	Co-segregation in multiple affected family members has not been reported for this variant.
PM1		✖	This variant does not involve one of the specific residues known to be crucial to the function of IDUA.
PM5		✖	A single different missense variant (c.224C>T causing p.Ala75Val) in the same codon have been reported in ClinVar (Variation ID 1464729). However it is unclear whether it has been seen in any patients, and this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen Lysosomal Diseases VCEP.
PM4		✖	This is a missense variant: this criterion does not apply.
PM6		✖	This variant has not been reported as a de novo change.
BS2		✖	This variant is not seen in the homozygous state in any controls in gnomAD v4.0.
PS1		✖	No other established pathogenic variants are reported with the same amino acid change.
PS2		✖	This variant has not been reported as a de novo change.
BP3		✖	This is a missense variant: this criterion does not apply.
BP5		✖	There is no known alternate molecular basis for deficiency of alpha-L-iduronidase activity, other than variants in IDUA.
BP7		✖	This is a missense variant: this criterion does not apply.

Curation History



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