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Variant: NM_000203.5(IDUA):c.653T>C (p.Leu218Pro)

Version: 1.0

CA356986

222995 (ClinVar)

Gene: IDUA
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: d26fc997-21d5-45e8-9215-87315dbf8f3f
Approved on: 2025/12/14
Published on: 2025/12/28

HGVS expressions

NM_000203.5(IDUA):c.653T>C (p.Leu218Pro)
NM_000203.5(IDUA):c.653T>C
NM_000203.5:c.653T>C
NC_000004.12:g.1001742T>C
CM000666.2:g.1001742T>C
NC_000004.11:g.995530T>C
CM000666.1:g.995530T>C
NC_000004.10:g.985530T>C
NG_008103.1:g.19746T>C
ENST00000247933.9:c.653T>C
ENST00000514224.2:c.653T>C
ENST00000652070.1:n.709T>C
ENST00000247933.8:c.653T>C
ENST00000502910.5:c.512T>C
ENST00000509948.5:c.446T>C
ENST00000514192.5:c.470T>C
ENST00000514224.1:c.257T>C
ENST00000514698.5:n.553T>C
NM_000203.4:c.653T>C
NR_110313.1:n.741T>C
NM_001363576.1:c.257T>C

Pathogenic

Met criteria codes 5

PM3_Very Strong | PS3_Supporting | PP3_Moderate | PP4 | PM2_Supporting

Not Met criteria codes 1

PM5

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_000203.4:c.653T>C variant in IDUA is a missense variant predicted to cause substitution of Leucine by Proline at amino acid 218 (p.Leu218Pro). This variant has been detected in at least 12 individuals with MPS I. Of those individuals, at least 9 were compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I based on classification by the ClinGen LD VCEP; specifically, at least 6 were compound heterozygous for the variant and c.208C>T (p.Gln70Ter) (PMID: 7951228, 23837464, 29906569) (ClinVar Variation ID: 11909, phase unconfirmed, max 1 point), 1 was compound heterozygous for the variant and c.159C>A (p.Cys53Ter) (PMID: 34547335) (ClinVar Variation ID: 1458768) (phase unconfirmed, 0.5 points), and at least 2 were compound heterozygous for the variant and c.1205G>A (p.Trp402Ter) (PMID: 7951228, 23837464, 29906569) (ClinVar Variation ID: 11908). At least one of the patients with c.1205G>A (p.Trp402Ter) also carried a third variant, c.299+6C>T (PMID: 22976768) (referred to as G387+6c->t in PMID: 7951228) on the same allele as p.Leu218Pro, indicating that p.Leu218Pro and p.Trp402Ter are in trans (1 point). Of note, c.299+6C>T is benign based on classification by the ClinGen LD VCEP. The phase is unknown for the other patient with p.Trp402Ter (0.5 points). At least 2 individuals were found to be homozygous for the variant (PMID: 7951228, 23837464, 29906569, max 1 point). Another individual was found to be compound heterozygous for the variant and c.943G>T (p.Asp315Tyr) (PMID: 23837464). The allelic data from this patient will be used to support the classification of p.Asp315Tyr and is not included here to avoid circular logic. Total 4 points (PM3_Very Strong). Ten patients were recorded with this variant (PMID: 23837464, PMID: 34547335). Of the nine in (PMID: 23837464), eight were reported to have a clinical phenotype of Hurler and one was reported to have a clinical phenotype of Hurler/Scheie. Five had their enzyme levels recorded and all had deficient IDUA levels. Urine GAGs were measured but results were not reported. Five had upper respiratory tract involvement; four were checked for an inguinal hernia but were found to be absent. Patient 1 in (PMID: 34547335) underwent HSCT at 14.1 months. (PP4). The computational predictor REVEL gives a score of 0.918 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). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00002 (25/1178218 alleles) in the Non-Finnish European population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). Expression of the variant in HEK293 cells resulted in a relative specific activity of 0.40% when compared to wild type IDUA, and significantly reduced processing on Western blot. indicating that this variant may impact protein function (PIMD:39702574)(PS3_Supporting). There is a ClinVar entry for this variant (Variation ID:222995). In summary, this variant meets the criteria to be classified as pathogenic for MPS I based on the IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 1.1.0): PM3_Very Strong, PP3_Moderate, PP4, PS3_Supporting, PM2_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 14, 2025)

Met criteria codes

PM3_Very Strong	✔	This variant has been detected in at least 12 individuals with MPS I. Of those individuals, at least 9 were compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I based on classification by the ClinGen LD VCEP; specifically, at least 6 were compound heterozygous for the variant and c.208C>T (p.Gln70Ter) (PMID: 7951228, 23837464, 29906569) (ClinVar Variation ID: 11909, phase unconfirmed, max 1 point), 1 was compound heterozygous for the variant and c.159C>A (p.Cys53Ter) (PMID: 34547335) (ClinVar Variation ID: 1458768) (phase unconfirmed, 0.5 points), and at least 2 were compound heterozygous for the variant and c.1205G>A (p.Trp402Ter) (PMID: 7951228, 23837464, 29906569) (ClinVar Variation ID: 11908). At least one of the patients with c.1205G>A (p.Trp402Ter) also carried a third variant, c.299+6C>T (PMID: 22976768) (referred to as G387+6c->t in PMID: 7951228) on the same allele as p.Leu218Pro, indicating that p.Leu218Pro and p.Trp402Ter are in trans (1 point). Of note, c.299+6C>T is benign based on classification by the ClinGen LD VCEP. The phase is unknown for the other patient with p.Trp402Ter (0.5 points). At least 2 individuals were found to be homozygous for the variant (PMID: 7951228, 23837464, 29906569, max 1 point). Another individual was found to be compound heterozygous for the variant and c.943G>T (p.Asp315Tyr) (PMID: 23837464). The allelic data from this patient will be used to support the classification of p.Asp315Tyr and is not included here to avoid circular logic. Total 4 points (PM3_Very Strong).

PS3_Supporting		✔	Expression of the variant in HEK293 cells resulted in a relative specific activity of 0.40% when compared to wild type IDUA, and significantly reduced processing on Western blot. indicating that this variant may impact protein function (PIMD:39702574)(PS3_Supporting).
PP3_Moderate		✔	The computational predictor REVEL gives a score of 0.918 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		✔	Ten patients were recorded with this variant (PMID: 23837464, PMID: 34547335). Of the nine in (PMID: 23837464), eight were reported to have a clinical phenotype of Hurler and one was reported to have a clinical phenotype of Hurler/Scheie. Five had their enzyme levels recorded and all had deficient IDUA levels. Urine GAGs were measured but results were not reported. Five had upper respiratory tract involvement; four were checked for an inguinal hernia but were found to be absent. Patient 1 in (PMID: 34547335) underwent HSCT at 14.1 months (PP4).
PM2_Supporting		✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00002 (25/1178218 alleles) in the Non-Finnish European population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5		✖	The variant c.653T>C is the only variant found in this codon in ClinVar; therefore no impact on splicing.

Curation History

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