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.1487C>T (p.Pro496Leu)

Version: 1.0

CA91170412

551675 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 908872f6-16c3-4ea1-b88d-ad0561b4fe37
Approved on: 2024/12/6
Published on: 2024/12/16

HGVS expressions

NM_000203.5(IDUA):c.1487C>T (p.Pro496Leu)
NM_000203.5:c.1487C>T
NC_000004.12:g.1003120C>T
CM000666.2:g.1003120C>T
NC_000004.11:g.996908C>T
CM000666.1:g.996908C>T
NC_000004.10:g.986908C>T
NG_008103.1:g.21124C>T
ENST00000247933.9:c.1487C>T
ENST00000514224.2:c.1487C>T
ENST00000652070.1:n.1543C>T
ENST00000247933.8:c.1487C>T
ENST00000502829.1:n.289C>T
ENST00000514224.1:c.1091C>T
ENST00000514698.5:n.1594C>T
NM_000203.4:c.1487C>T
NR_110313.1:n.1575C>T
NM_001363576.1:c.1091C>T

Likely Pathogenic

Met criteria codes 5

PP3 PM3 PM2_Supporting PS3_Supporting PM5_Supporting

Not Met criteria codes 5

PP1 PP4 PM6 PS1 PS2

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.1487C>T variant in IDUA is a missense variant predicted to cause substitution of proline by leucine at amino acid 496, p.(Pro496Leu). This variant has been reported to account for 0.65% of disease-causing alleles in individuals with MPS I (PMIDs: 28752568, 7550232, 18463126). At least two probands have been reported to be compound heterozygous, phase not confirmed, for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen LD VCEP, c.1205G>A (p.Trp402Ter) (PMID:18463126, 28752568). Another patient has been reported who is compound heterozygous for the variant and c.223G>A (p.Ala75Thr) (PMID: 7550232). The allelic data for this patient will be used in the classification of p.Ala75Thr and is not included here to avoid circular logic (PM3 applied; insufficient evidence to apply PP4). The highest population minor allele frequency in gnomAD v4.1.0. is 0.000012 (1/80558 alleles) in the South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). When the variant was expressed in Cos-1 cells, IDUA activity was absent (PMID: 7550232) (PS3_Supporting). Computational predictor tools (REVEL score 0.647) suggest that this variant may be deleterious to IDUA function (PP3). In addition, a different missense variant, c.1487C>G (p.Pro496Arg) [ClinVar Variation ID 496861] in the same codon has been classified as likely pathogenic for MPS I by the ClinGen LD VCEP (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 551675). In summary, this variant meets the criteria to be classified as likely pathogenic for MPS I based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 1.0.0): PS3_Supporting, PM2_Supporting, PM3, PM5_Supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 6, 2024)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.647 which is in the range 0.644-0.773, evidence that correlates with impact to IDUA function at the supporting level (PMID: 36413997) (PP3). SpliceAI predicts that the variant has no impact on splicing.
PM3	✔	At least two probands have been reported to be compound heterozygous, phase not confirmed, for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen LD VCEP including c.1205G>A (p.Trp402Ter) (PMID:18463126, 28752568) (phase not confirmed, 2 x 0.5 points). Another patient has been reported who is compound heterozygous for the variant and c.223G>A (p.Ala75Thr) (PMID: 7550232). The allelic data for this patient will be used in the classification of p.Ala75Thr and is not included here to avoid circular logic. Total 1 point (PM3)
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.000012 (1/80558 alleles) in the South Asian 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, indicating that this variant may impact protein function (PMID: 7550232)(PS3_Supporting).
PM5_Supporting	✔	Another missense variant [c.1487C>G | p.(Pro496Arg)] [ClinVar Variation ID 496861] in the same codon has been classified as likely pathogenic for MPS I by the ClinGen LD VCEP (PM5_Supporting).

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	In the above reported cases, biochemical or clinical results demonstrating specificity of the diagnosis were not presented.

PM6		✖	This variant has not been reported as a de novo change.
PS1	ℹ	✖	No other established pathogenic variants are reported with the same amino acid change.
PS2	ℹ	✖	This variant has not been reported as a de novo change.

Curation History

owing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.