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.1577T>C (p.Leu526Pro)

Version: 1.1

CA2802300

567566 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: af82e2af-5547-407b-8cd9-130a5121d52f
Approved on: 2025-04-21
Published on: 2025-08-07

HGVS expressions

NM_000203.5:c.1577T>C
NM_000203.5(IDUA):c.1577T>C (p.Leu526Pro)
NC_000004.12:g.1003397T>C
CM000666.2:g.1003397T>C
NC_000004.11:g.997185T>C
CM000666.1:g.997185T>C
NC_000004.10:g.987185T>C
NG_008103.1:g.21401T>C
ENST00000247933.9:c.1577T>C
ENST00000514224.2:c.1577T>C
ENST00000652070.1:n.1633T>C
ENST00000247933.8:c.1577T>C
ENST00000514224.1:c.1181T>C
ENST00000514698.5:n.1684T>C
NM_000203.4:c.1577T>C
NR_110313.1:n.1665T>C
NM_001363576.1:c.1181T>C

Uncertain Significance

Met criteria codes 3

PP4 PM3 PP3_Moderate

Not Met criteria codes 4

BS1 BS3 PS3 PM2

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.1577T>C variant in IDUA is a missense variant predicted to cause substitution of leucine by proline at amino acid 526 (p.Leu526Pro). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0005078 (42/82710 alleles) in the South Asian population. This is higher than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), and lower than the threshold for BS1 (>0.0025). Therefore, none of the population data codes are met. At least 12 individuals have been reported with biallelic variants in IDUA (not including pseudodeficiency variants). Eight of those individuals were identified by a newborn screen, all with low IDUA activity, but all with normal total GAGs, and either normal or mildly elevated dermatan and heparan sulfate; two of these individuals were described as having an attenuated phenotype based on clinical evaluation, and others as suspected or undetermined diagnosis (30442156, 30093709, 32432561, 33072983, 33147872, 35787971, 37516270, Greenwood Genetic Center). At least 3 other individuals have been reported to have symptoms consistent with MPS I (22976768, 26260077, 31194252, 37181073). One individual with the variant has been reported with an extremely attenuated phenotype (PMID: 37181073). This individual, who is compound heterozygous for the variant and c.228T>A (p.Tyr76Ter), confirmed in trans by parental testing (1 point for PM3), was diagnosed with MPS I at age 38 years. She presented with valvular disease, retinopathy, short stature, dysostosis multiplex, and coarse facial features, and had deficient IDUA activity and elevated urine and serum dermatan and heparan sulfate (elevations were mild) (PP4 met based on clinical symptoms and IDUA deficiency). Another patient, reported to be on ERT and to have skeletal features of MPS I (PMID: 26260077, 31194252; may be the same patient in both papers) is compound heterozygous for the variant and c.1205G>A (p.Trp402Ter) (PMID: 26260077, 3119425) in unknown phase (0.5 points for PM3). Data from another patient, compound heterozygous for the variant and p.Gln70Ter, were not included due to lack of GAG levels, and the presence of a pseudodeficiency variant (PMID: 22976768; personal communication). Total 1.5 points (PM3) However, 27-year-old female, who is compound heterozygous for p.Leu526Pro and c.1205G>A (p.Tyr402Ter), confirmed in trans, has no clinical features of MPS I based on detailed physical exam. Although she has elevated NRE marker UA-HNAc(1S), the elevation is not of the degree observed in affected individuals (PMID: 39702574). Similarly, a 7-month-old with the same genotype also has elevated NRE marker UA-HNAc(1S), but not in the range typically associated with MPS I (PMID: 39702574) (Total 1.5 points, PM3). PP4 was applied based on the reported features of MPS I in some patients. The computational predictor REVEL gives a score of 0.774 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 the variant was expressed in IDUA knock-out HEK293 cells, the relative specific activity (activity of IDUA/amount of IDUA protein) was 15% of wild type activity (3 times higher than the activity of the "pseudodeficiency" variant, p.Ala79Thr, which is clinically benign). However, the p.Leu526Pro IDUA protein exhibits impaired proteolytic processing on Western blot, and evidence of aggregation of native gel electrophoresis. Based on the relatively high activity, but abnormalities in processing and aggregation, neither PS3 nor BS3 is met. There is a ClinVar entry for this variant (Variation ID: 567566). In summary, currently, the clinical impact of p.Leu526Pro is unclear (variant of uncertain significance), particularly given the reports of some patients with a diagnosis of MPS I, and others with normal total GAG levels and reports of only mild elevations of dermatan and heparan sulfate (PMID: 39702574, Greenwood Genetic Center). This could suggest that the variant has reduced penetrance; however additional data is required to fully understand the clinical impact of this variant. IDUA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 1.0.0.): PM3, PP3_Moderate, PP4. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, April 21, 2025).

Met criteria codes

PP4 ✔

At least 12 individuals have been reported with biallelic variants in IDUA (not including pseudodeficiency variants). Eight of those individuals were identified by a newborn screen, all with low IDUA activity, but all with normal total GAGs, and either normal or mildly elevated dermatan and heparan sulfate; two are described as having an attenuated phenotype based on clinical evaluation, others as suspected or undetermined diagnosis (30442156, 30093709, 32432561, 33072983, 33147872, 35787971, 37516270, Greenwood Genetic Center). At least 3 other individuals have been reported with symptoms consistent with MPS I (22976768, 26260077, 31194252, 37181073). One individual with the variant has been reported with an extremely attenuated phenotype (PMID: 37181073). This individual, who is compound heterozygous for the variant and c.228T>A (p.Tyr76Ter), confirmed in trans by parental testing (PM3, 1 point), was diagnosed with MPS I at age 38 years. She presented with valvular disease, retinopathy, short stature, dysostosis multiplex, and coarse facial features, and had deficient IDUA activity and elevated urine and serum dermatan and heparan sulfate (although some elevations were mild) (PP4 met based on clinical symptoms and IDUA deficiency). Another patient, reported to be on ERT and to have skeletal features of MPS I (PMID: 26260077, 31194252; may be the same patient in both papers) is compound heterozygous for the variant and c.1205G>A (p.Trp402Ter) (PMID: 26260077, 3119425) in unknown phase (PM3, 0.5 points). However, 27-year-old female, who is compound heterozygous for p.Leu526Pro and c.1205G>A (p.Tyr402Ter), confirmed in trans, has

no clinical features of MPS I based on detailed physical exam. Although she has elevated NRE marker UA-HNAc(1S), the elevation is not of the degree observed in affected individuals. Similarly, a 7-month-old with the same genotype also has elevated NRE marker UA-HNAc(1S), but not in the range typically associated with MPS I. PP4 was applied based on the reported features of MPS I in some patients. However, the clinical impact of the variant is unclear, particularly given the reports of some patients with a diagnosis of MPS I (GAG levels not reported), and others with normal total GAG levels and reports of only mild elevations of dermatan and heparan sulfate, not in the range of known affected individuals, even in an adult who is compound heterozygous for the variant confirmed in trans with pathogenic variant, c.1205G>A (p.Trp402Ter) (PMID: 39702574, Greenwood Genetic Center) (PP4).

PM3	✔	Although multiple individuals have been reported with the variant (see PP4), due to the lack of evidence supporting the diagnosis of MPS I, allelic data will not be included for those patients. One patient, exhibiting very mild features of MPS I was compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic for MPS I by the ClinGen LD VCEP, c.228T>A (p.Tyr76Ter); the variants, which were identified by whole genome sequencing, were confirmed to be in trans by parental testing (PMID: 37181073, 1 point). Another patient, who is in the MPS I registry, is compound heterozygous for the variant and c.1205G>A (p.Trp402Ter) (PMID: 26260077, 31194252; may be the same patient in both papers); phase unknown (0.5 points). Data from another patient, compound heterozygous for the variant and p.Gln70Ter, were not included due to lack of GAG levels and presence of a pseudodeficiency variant (PMID: 22976768; personal communication). Total 1.5 points (PM3)
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.774 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

BS1	✖	The highest population minor allele frequency in gnomAD v4.1 is 0.0005078 (42/ 82710 alleles) in the South Asian population. This is higher than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), and lower than the threshold for BS1 (>0.0025). Therefore, none of the population data codes are met.
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	When the variant was expressed in IDUA knock-out HEK293 cells, the relative specific activity (activity of IDUA/amount of IDUA protein) was 15% of wild type activity (3 times higher than the activity of the "pseudodeficiency" variant, p.Ala79Thr, which is clinically benign). However, the p.Leu526Pro IDUA protein exhibits impaired proteolytic processing on Western blot, and evidence of aggregation of native gel electrophoresis. based on the relatively high activity, but abnormalities in processing and aggregation, neither PS3 nor BS3 is met.
PM2	✖	The highest population minor allele frequency in gnomAD v4.1 is 0.0005078 (42/ 82710 alleles) in the South Asian population. This is higher than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), and lower than the threshold for BS1 (>0.0025). Therefore, none of the population data codes are met.

Curation History