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.536C>T (p.Thr179Met)

Version: 1.0

CA2801986

1455223 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0f7c71ac-becf-4524-b8e1-5184f56b8916
Approved on: 2024/12/6
Published on: 2024/12/15

HGVS expressions

NM_000203.5:c.536C>T
NM_000203.5(IDUA):c.536C>T (p.Thr179Met)
NC_000004.12:g.1001510C>T
CM000666.2:g.1001510C>T
NC_000004.11:g.995298C>T
CM000666.1:g.995298C>T
NC_000004.10:g.985298C>T
NG_008103.1:g.19514C>T
ENST00000247933.9:c.536C>T
ENST00000514224.2:c.536C>T
ENST00000652070.1:n.592C>T
ENST00000247933.8:c.536C>T
ENST00000502910.5:c.395C>T
ENST00000504568.5:c.496C>T
ENST00000509948.5:c.329C>T
ENST00000514192.5:c.353C>T
ENST00000514224.1:c.140C>T
ENST00000514698.5:n.436C>T
NM_000203.4:c.536C>T
NR_110313.1:n.624C>T
NM_001363576.1:c.140C>T

Likely Pathogenic

Met criteria codes 3

PM3 PP3_Moderate PP4_Moderate

Not Met criteria codes 2

PM5 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.536C>T variant in IDUA is predicted to result in a missense substitution, p.Thr179Met. One patient is compound heterozyous for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.1205G>A or (p.Trp402Ter); the variants were identified by trio exome sequencing are are confirmed to be in trans (PMID: 32670797) (PM3). This patient has documented values showing deficient IDUA activity in two independent samples, elevated urine GAGs with high levels of heparan and dermatan sulfate which reduced to only a trace after 12 months of enzyme replacement therapy, and clinical symptoms consistent with the condition (PMID: 32670797) (PP4_Moderate). The highest population minor allele frequency (MAF) in gnomAD v2.1.1 is 0.0002 (5/25114 alleles) in the Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion. The next highest population MAF is 0.00003 (4/128740 alleles) in the European non-Finnish population (PM2_Supporting). Other missense variants at the same position have been reported in individuals with MPS1, including c.536C>G (p.Thr179Arg) (PMID: 21480867), and p.Thr179Lys (PMID: 28752568). The classification of c.536C>T (p.Thr179Met) will be used in the assessment of the other variants at Thr179 and is not included here to avoid circular logic. There is a ClinVar entry for this variant (ClinVar ID: 1455223). In summary, this variant meets the criteria to be classified as likely pathogenic. IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 1.0.0): PM3, PP3_Moderate, PP4_Moderate, PM2_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 6, 2024)

Met criteria codes

PM3	✔	One patient is compound heterozyous for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen LD VCEP, c.1205G>A or (p.Trp402Ter); the variants were identified by trio exome sequencing are are confirmed to be in trans (PMID: 32670797). 1 point (PM3).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.844 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	✔	At least two individuals with this variant have been identified including one, identified by trio whole exome sequencing, with documented values showing deficient IDUA activity in two samples, elevated urine GAGs with high levels of heparan and dermatan sulfate which reduced to only a trace after 12 months of enzyme replacement therapy, and clinical symptoms consistent with the condition (PMID: 32670797) (PP4_Moderate).

Not Met criteria codes

PM5	✖	Other missense variants at the same position have been reported in individuals with MPS1, including c.536C>G (p.Thr179Arg) (PMID: 21480867), and p.Thr179Lys (PMID: 28752568). The classification of c.536C>T (p.Thr179Met) will be used in the assessment of the other variants at Thr179 and is not included here to avoid circular logic.
PM2	✖	The highest population minor allele frequency (MAF) in gnomAD v4.1.0. is 0.0003482 (22/63178 alleles; no homozygotes) in the Finnish population, which is higher than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), not meeting this criterion. The next highest population MAF is 0.00002627 (31/1179960 alleles; no homozygotes) in the European non-Finnish population.

Curation History





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