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Variant: NM_000203.5(IDUA):c.1882C>T (p.Arg628Ter)

Version: 1.0

CA2802462

550421 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9e100608-b0d6-4fc2-a65b-17ddfc4bad5a
Approved on: 2025/7/7
Published on: 2025/7/17

HGVS expressions

NM_000203.5(IDUA):c.1882C>T (p.Arg628Ter)
NM_000203.5:c.1882C>T
NC_000004.12:g.1004313C>T
CM000666.2:g.1004313C>T
NC_000004.11:g.998101C>T
CM000666.1:g.998101C>T
NC_000004.10:g.988101C>T
NG_008103.1:g.22317C>T
ENST00000247933.9:c.1882C>T
ENST00000514224.2:c.1882C>T
ENST00000652070.1:n.1938C>T
ENST00000247933.8:c.1882C>T
ENST00000514224.1:c.1486C>T
ENST00000514698.5:n.1993C>T
NM_000203.4:c.1882C>T
NR_110313.1:n.1974C>T
NM_001363576.1:c.1486C>T

Pathogenic

Met criteria codes 4

PM3_Very Strong | PP4_Moderate | PVS1_Moderate | PM2_Supporting

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(IDUA):c.1882C>T (p.Arg628Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in the last exon of the gene and therefore to escape nonsense mediated decay. Less than 10% of the protein is predicted to be removed (PVS1_Moderate). This variant has been detected in at least 16 individuals with MPS I. This variant has been detected in at least 17 individuals with MPS I. Of those individuals, 6 were compound heterozygous for the variant and a variant that has been classified as pathogenic or likely pathogenic for MPS I by the ClinGen LD VCEP, including c.236C>T (p.Ala79Val) (ClinVar Variation ID: 1458769) (PMID: 27520059, LP, 0.25 pts); c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (PMID: 15081804, 25614311, 2 x 0.5 pts); c.208C>T (p.Gln70Ter) (ClinVar Variation ID: 11909) (PMID: 12509712, 19396826, 19954743; one confirmed in trans, one unconfirmed, 1 + 0.5 pt) and c.2T>C (p.Met1?) (PMID: 34813777, 0.5 pts). Ten individuals were homozygous for the variant (PMIDs: 27511503, 24798265, 21521498, 12203999, 11735025, 35141277, 35893030, 22718273, 35123515) (max 2 x 0.5 pt). Another proband was compound heterozygous for the variant and c.809T>G (p.Ile270Ser) (PMID: 16435195); the allelic data from this patient has been used in the classification of p.Ile270Ser and is not included here to avoid circular logic. Total 4.25 pts (PM3_VeryStrong). At least 4 patients with this variant had documented IDUA deficiency within the affected range in leukocytes and/or clinical features specific to MPS I including dysostosis multiplex, hepatosplenomegaly, and corneal involvement (PMIDs: 27520059, 21521498, 19396826, 11735025; PP4_Moderate). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00004459 (2/44852 alleles) in the East Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). To our knowledge, the results of functional assays have not been reported for this variant. There is a ClinVar entry for this variant (Variation ID: 550421). 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 1.0.0): PM3_VeryStrong, PVS1_Moderate, PP4_Moderate, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on July 7, 2025)

Met criteria codes

PM3_Very Strong	✔	This variant has been detected in at least 17 individuals with MPS I. Of those individuals, 6 were compound heterozygous for the variant and a variant that has been classified as pathogenic or likely pathogenic for MPS I by the ClinGen LD VCEP, including c.236C>T (p.Ala79Val) (ClinVar Variation ID: 1458769) (PMID: 27520059, LP, 0.25 pts); c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (PMID: 15081804, 25614311, 2 x 0.5 pts); c.208C>T (p.Gln70Ter) (ClinVar Variation ID: 11909) (PMID: 12509712, 19396826, 19954743; one confirmed in trans, one unconfirmed, 1 + 0.5 pt), and c.2T>C (p.Met1?) (PMID: 34813777, 0.5 pts). Ten individuals were homozygous for the variant (PMIDs: 27511503, 24798265, 21521498, 12203999, 11735025, 35141277, 35893030, 22718273, 35123515) (max 2 x 0.5 pt). Another proband was compound heterozygous for the variant and c.809T>G (p.Ile270Ser); the allelic data from this patient has been used in the classification of p.Ile270Ser and is not included here to avoid circular logic. Total 4.25 pts (PM3_VeryStrong).
PP4_Moderate	✔	At least 6 patients with this variant had documented IDUA deficiency within the affected range in leukocytes and/or clinical features specific to MPS I including dysostosis multiplex, hepatosplenomegaly, and corneal involvement (PMIDs: 27520059, 21521498, 19396826, 11735025, 16435195, 35141277) (PP4_Moderate).
PVS1_Moderate	✔	The NM_000203.5(IDUA):c.1882C>T (p.Arg628Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in the last exon of the gene and therefore to escape nonsense mediated decay. Less than 10% of the protein is predicted to be removed (PVS1_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00004459 (2/44852 alleles) in the East Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).

Curation History



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