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Variant: NM_000203.5(IDUA):c.1883G>C (p.Arg628Pro)

Version: 1.0

CA2802464

1064675 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5b06d215-7444-4f08-bce3-9eedaff7c66d
Approved on: 2025/12/21
Published on: 2025/12/29

HGVS expressions

NM_000203.5(IDUA):c.1883G>C (p.Arg628Pro)
NM_000203.5:c.1883G>C
NC_000004.12:g.1004314G>C
CM000666.2:g.1004314G>C
NC_000004.11:g.998102G>C
CM000666.1:g.998102G>C
NC_000004.10:g.988102G>C
NG_008103.1:g.22318G>C
ENST00000247933.9:c.1883G>C
ENST00000514224.2:c.1883G>C
ENST00000652070.1:n.1939G>C
ENST00000247933.8:c.1883G>C
ENST00000514224.1:c.1487G>C
ENST00000514698.5:n.1994G>C
NM_000203.4:c.1883G>C
NR_110313.1:n.1975G>C
NM_001363576.1:c.1487G>C

Likely Pathogenic

Met criteria codes 5

PM3_Supporting | PS3_Moderate | PP4_Moderate | PM2_Supporting | PP3

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_000203.5:c.1883G>C variant in IDUA is a missense variant that is predicted to result in the substitution of arginine by proline at amino acid 628 (p.Arg628Pro). Two patients with a diagnosis of MPS I, both of German origin, have been reported with the variant. A detailed report was available for one of these patients who had attenuated disease with documented low levels of IDUA activity in plasma and leukocytes, clinical symptoms consistent with MPS I, and elevated CSF GAG levels which decreased into the normal range after intrathecal ERT (PMID: 18792977) (PP4_Moderate). This patient is compound heterozygous for the variant and another variant in IDUA that has been classified by the ClinGen LD VCEP as pathogenic for MPS I, c.1139A>G (p.Gln380Arg). The phase is unknown (PMID: 12559846, 18792977). The second patient is compound heterozygous for the variant and c.979G>C (p.Ala327Pro). The allelic data from the second patient will be used in the classification of p.Ala327Pro and is not included here to avoid circular logic. Total points = 0.5 (PM3_Supporting). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001336 (1/74840 alleles) in the African/African American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). When expressed in CHO cells, the variant had <1% activity in cell lysate compared to WT (Table 4) and significantly reduced amount of protein with reduced processing on Western blot (Fig. 1) (PMID: 12559846). The computational predictor REVEL gives a score of 0.667 which is in the range 0.644-0.773, evidence that correlates with impact to IDUA function at the supporting level (PMID: 36413997) (PP3). There is a ClinVar entry for this variant (Variation ID: 1064675). In summary, this variant meets the criteria to be classified as pathogenic for mucopolysaccharidosis type I. IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert panel (Specifications Version 1.1.0): PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Disease Variant Curation Expert Panel on December 21, 2025)

Met criteria codes

PM3_Supporting	✔	One patient is compound heterozygous for the variant and another variant in IDUA that has been classified by the ClinGen LD VCEP as pathogenic for MPS I, c.1139A>G (p.Gln380Arg). The phase is unknown (PMID: 12559846, 18792977). Another patient is compound heterozygous for the variant and c.979G>C (p.Ala327Pro). The allelic data from the second patient will be used in the classification of p.Ala327Pro and is not included here to avoid circular logic. Total points = 0.5 (PM3_Supporting)
PS3_Moderate	✔	When expressed in CHO cells, the variant had <1% activity in cell lysate compared to WT (Table 4) and significantly reduced amount of protein with reduced processing on Western blot (Fig. 1) (PMID: 12559846)
PP4_Moderate	✔	Two patients with a diagnosis of MPS I, both of German origin, have been reported with the variant. A detailed report was available for one of these patients who had attenuated disease with documented low levels of IDUA activity in plasma and leukocytes, clinical symptoms consistent with MPS I, and elevated CSF GAG levels which decreased into the normal range after intrathecal ERT (PMID: 18792977) (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001336 (1/74840 alleles) in the African/African American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.667 which is in the range 0.644-0.773, evidence that correlates with impact to IDUA function at the supporting level (PMID: 36413997) (PP3).

Curation History

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