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Variant: NM_000203.5(IDUA):c.603C>G (p.Tyr201Ter)

Version: 1.0

CA355961899

1323100 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7e224408-fb91-49f8-9218-48e07c8d2739
Approved on: 2025/7/7
Published on: 2025/7/17

HGVS expressions

NM_000203.5:c.603C>G
NM_000203.5(IDUA):c.603C>G (p.Tyr201Ter)
NC_000004.12:g.1001692C>G
CM000666.2:g.1001692C>G
NC_000004.11:g.995480C>G
CM000666.1:g.995480C>G
NC_000004.10:g.985480C>G
NG_008103.1:g.19696C>G
ENST00000247933.9:c.603C>G
ENST00000514224.2:c.603C>G
ENST00000652070.1:n.659C>G
ENST00000247933.8:c.603C>G
ENST00000502910.5:c.462C>G
ENST00000504568.5:c.563C>G
ENST00000509948.5:c.396C>G
ENST00000514192.5:c.420C>G
ENST00000514224.1:c.207C>G
ENST00000514698.5:n.503C>G
NM_000203.4:c.603C>G
NR_110313.1:n.691C>G
NM_001363576.1:c.207C>G

Pathogenic

Met criteria codes 4

PVS1 PM3 PP4_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.603C>G (p.Tyr201Ter) is a nonsense variant predicted to cause a premature stop codon in exon 6 out of a total of 14 exons, leading to nonsense-mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The variant has been detected in at least four probands with MPS I. Of these individuals, one 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.46_57del (ClinVar Variation ID: 92643) (PMID: 21394825, 33072983, 1 patient 1 x 0.5 points, phase unknown). Two individuals were homozygous for the variant (max 2 x 0.5). (Total 1.5 points, PM3_Moderate). Another patient was compound heterozygous for the variant and c.-14_10del (PMID: 21394825). The allelic data from this patient will be used in the classification of c.-14_10del and is not included here to avoid circular logic. Of these patients, MPS I was confirmed in one newborn female with very low enzyme activity in leucocytes, high excretion of urine heparan sulphate and dermatan sulphate (DS) and clinical features of a severe Hurler phenotype (PMID: 33072983, 33147872, PMID: 32432561), Another patient, a 2.5 year old female of Italian origin had clinical features of a severe form of the disease at 15 days of age, and elevated urinary GAGs (PP4_Moderate). The highest population minor allele frequency in gnomAD v4.1 is 0.000000848 (1/1,179,052 alleles) in the European (non-Finnish) population; this is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025) meeting this criterion (PM2_Supporting). 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 Disease Variant Curation Expert Panel (Specifications Version 1.0.0): PVS1, PM3, PP4_Moderate, PM2_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on July 7, 2025).

Met criteria codes

PVS1	✔	The NM_000203.5(IDUA):c.603C>G (p.Tyr201Ter) is a nonsense variant predicted to cause a premature stop codon in exon 6 out of a total of 14 exons, leading to nonsense-mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM3	✔	The variant has been detected in at least four probands with MPS1. Of these individuals, one 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.46_57del (ClinVar Variation ID: 92643) (PMID: 21394825, 33072983, 1 patient 1 x 0.5 points due to phase unknown). Two individuals were homozygous for the variant (max 2 x 0.5). PM3_Moderate, total 1.5 points. Another patient was compound heterozygous for the variant and c.-14_10del (PMID: 21394825). The allelic data from this patient will be used in the classification of c.-14_10del and is not included here to avoid circular logic.
PP4_Moderate	✔	MPS I was confirmed in one newborn female with very low enzyme activity in leucocytes of 1.6% and high excretion of heparan sulfate (HS) at 220.6 (nv < 4.6) and dermatan sulfate (DS) at 90.6 (nv < 38.1) in urine, had clinical features of a severe Hurler phenotype (PMID: 33072983). More studies report the same case (PMID: 33147872, PMID: 32432561), a female of Italian origin is now 2.5 years old. On initial examination at 15 days of life, she had clinical features of a severe form of the disease: corneal clouding, coarse facial features, moderate sensorineural hearing loss, poor growth, rounding of the iliac wings, and large cisterna magna at brain MRI. This phenotype was confirmed by elevated urinary GAGs (HS 121.9 mg/mMol creatinine, nv < 4.6; DS 80.0 mg/mMol creatinine, nv < 38.1) (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.000000848 (1/1,179,052 alleles) in the European (non-Finnish) population; this is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025) meeting this criterion (PM2_Supporting).

Curation History



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.

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