Variant: NM_000203.5(IDUA):c.208C>T (p.Gln70Ter)

Version: 1.0

CA204563

11909 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 82f2cc6b-74c1-47c7-9ca0-1d5148992608
Approved on: 2025-01-02
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HGVS expressions

NM_000203.5:c.208C>T
NM_000203.5(IDUA):c.208C>T (p.Gln70Ter)
NC_000004.12:g.987858C>T
CM000666.2:g.987858C>T
NC_000004.11:g.981646C>T
CM000666.1:g.981646C>T
NC_000004.10:g.971646C>T
NG_008103.1:g.5862C>T
NG_033042.1:g.10579G>A
ENST00000247933.9:c.208C>T
ENST00000398516.3:c.*975G>A
ENST00000514224.2:c.208C>T
ENST00000247933.8:c.208C>T
ENST00000361661.6:c.*975G>A
ENST00000398520.6:c.576+3270G>A
ENST00000502910.5:c.158+616C>T
ENST00000504568.5:c.206C>T
ENST00000506561.5:n.217C>T
ENST00000508168.5:n.177+616C>T
ENST00000514698.5:n.199+616C>T
ENST00000622731.4:c.576+3270G>A
NM_000203.4:c.208C>T
NM_022042.3:c.*975G>A
NM_134425.2:c.576+3270G>A
NM_213613.3:c.*975G>A
NR_110313.1:n.296C>T
NM_022042.4:c.*975G>A
NM_134425.3:c.576+3270G>A
NM_213613.4:c.*975G>A
NM_134425.4:c.576+3270G>A

Pathogenic

Met criteria codes 3

PVS1 PP4 PM3

Not Met criteria codes 2

PM2 BS1

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.208C>T (p.Gln70Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2 of a total of 14 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. An immunochemical assay performed in fibroblast lines from two individuals homozygous for the variant and three individuals compound heterozygous for the variant and p.Trp402Ter found no detectable IDUA protein (PMID: 1301941) (PVS1). This variant is the second most common variant identified in patients with mucopolysacchararidosis type 1 (MPS1), and is present mainly in Northern Europe, including Norway (54% of MPS1 alleles), Russia (42% of MPS1 alleles), Poland (30% of MPS1 alleles), and Austria (31% of MPS1 alleles) (Reviewed in PMID: 29393969). At least 14 homozygotes (max 0.5 x 2 points = 1 point) and at least 45 individuals who are compound heterozygous for the variant and a second variant in IDUA, including another well-known pathogenic variant, c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908), have been reported (PMID: 1301941, 7951228, 11735025, 28752568). The allelic data for many of these patients will be used in the classification of the second variant and is not included here to avoid circular logic. Therefore, only 1 point was awarded here, the maximum points for homozygotes (PM3). Patients meeting two of the requirements for PP4, IDUA deficiency and elevated urine GAG levels have been reported (PMID: 1301941) (PP4). The highest population minor allele frequency in gnomAD v4.1.0 is 0.002123 in the Finnish population, followed by 0.0005348 in the European non-Finnish population. This is higher than the Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025) and lower than the threshold for BS1 (>0.0025). Therefore, no population codes are met. More data is available in the literature but the classification of pathogenic has already been reached. There is a ClinVar entry for this variant (Variation ID: 11909). In summary, c.208C>T (p.Gln70Ter) is the second most frequent variant identified in patients with MPS1 and meets the criteria to be classified as pathogenic for this condition. IDUA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases VCEP (Specifications Version 1.0.0): PVS1, PM3, PP4. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on January 2, 2025)

Met criteria codes

PVS1	ℹ	✓	The NM_000203.5:c.208C>T (p.Gln70Ter) variant in IDUA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2 out of 14 total exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. An immunochemical assay performed in fibroblast lines from two individuals homozygous for the variant and three individuals compound heterozygous for the variant and p.Trp402Ter found no detectable IDUA protein (PMID: 1301941) (PVS1).
PP4	ℹ	✓	At least 14 homozygotes and at least 45 individuals have been reported in the literature including some patients meeting two of the requirements for PP4, IDUA deficiency and elevated urine GAG levels (PMID: 1301941).
PM3	ℹ	✓	At least 14 homozygotes (max 0.5 x 2 points = 1 point) and at least 45 individuals who are compound heterozygous for the variant and a second variant in IDUA, including another well-known pathogenic variant, c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908), have been reported (PMID: 1301941, 7951228, 11735025, 28752568).

The allelic data for many of these patients will be used in the classification of the second variant and is not included here to avoid circular logic. Therefore, only 1 point was awarded here, the maximum points for homozygotes (PM3).

Not Met criteria codes

PM2		✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.002123 in the Finnish population, followed by 0.0005348 in the European non-Finnish population. This is higher than the Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025) and, therefore, does not meet this criterion.
BS1	ℹ	✖	The highest population minor allele frequency in a continental population in gnomAD v2.1.1 is 0.00194 (48/24766 alleles) in the Finnish population. which is lower than the ClinGen LSD VCEP's threshold for BS1 (>0.0025). Therefore, BS1 is not met.

Curation History

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