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.46_57del (p.Ser16_Ala19del)*

Version: 1.0

*CA220509*

*92643 (ClinVar)*

**Gene**: IDUA (HGNC:3425)
**Condition**: mucopolysaccharidosis type 1 (MONDO:0001586)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** e5db4fa7-8a0e-4c1c-a085-0a9ba8f72efe
**Approved on**: 2024-12-06
**Published on**: 2024-12-15

## *HGVS expressions*

**NM_000203.5:c.46_57del**
NM_000203.5(IDUA):c.46_57del (p.Ser16_Ala19del)
NC_000004.12:g.987130_987141del
CM000666.2:g.987130_987141del
NC_000004.11:g.980918_980929del
CM000666.1:g.980918_980929del
NC_000004.10:g.970918_970929del
NG_008103.1:g.5134_5145del
NG_033042.1:g.11307_11318del
ENST00000247933.9:c.46_57del
ENST00000514224.2:c.46_57del
ENST00000247933.8:c.46_57del
ENST00000398520.6:c.576+3998_576+4009del
ENST00000502910.5:c.46_57del
ENST00000504568.5:c.44_55del
ENST00000506561.5:n.55_66del
ENST00000508168.5:n.65_76del
ENST00000514698.5:n.87_98del
ENST00000622731.4:c.576+3998_576+4009del
NM_000203.4:c.46_57del
NM_134425.2:c.576+3998_576+4009del
NR_110313.1:n.134_145del
NM_134425.3:c.576+3998_576+4009del
NM_134425.4:c.576+3998_576+4009del

**Pathogenic**

**Met criteria codes** 5

PP4 PM4 PM3_Very Strong PM2_Supporting PS3_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:c.46_57del variant results in an inframe deletion of 4 amino acids (p.Ser16_Ala19del) within the lysosomal signal sequence of IDUA (PM4). This variant is named "134del12" in older literature. At least twelve patients with with variant and a diagnosis of mucopolysaccharidosis type 1 have been reported in the literature. This includes four patients with documented laboratory values showing deficiency of IDUA activity in fibroblasts or leukocytes (PMID: 15300847, 21394825, 23786846) one of whom also had documented clinical features consistent with the diagnosis including corneal clouding, joint stiffness, digital contractures, cardiac valve disease, airway obstruction, and developmental delay (PMID: 15300847) (PP4). Four individuals have been reported who are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP including two confirmed in trans - c.1750C>T (p.Gln584Ter) (PMID: 12189649) and p.Trp402Ter (PMID: 11735025); and two phase unknown - c.208C>T (p.Gln70Ter) (PMID: 21394825) and c.386-2A>G (PMID: 11735025). In addition, at least two homozygotes have been reported PMID: 7951228, 21394825) (PM3_VeryStrong). Additional patients are compound heterozygous for the variant and c.603C>G (p.Tyr201Ter) (PMID: 21394825), c.1189+5G>A (PMID: 21394825); c.1960T>C (p.Ter654ArgextTer*62) (PMID: 21394825), c.1049A>T (p.Asn350Ile) (PMID: 12559846) and c.1598C>G (p.Pro533Arg) (PMID: 15300847). The allelic data from these patients will be used in the classification of the second variant and is not included here to avoid circular logic. When expressed in COS-7 cells, the variant (labeled as "134del12") resulted in 124.6% of normal activity. A 77-kDa precursor protein was observed on Western blot, compared with a major mature 63-kDa form and a minor 77-kDa precursor in cells transfected with wild-type cDNA. These results suggested that the variant prevents correct posttranslational processing and transport to the lysosome (PMID: 12189649) (PS3_Supporting). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00006251 (69/1103836 alleles) in the European non-Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 92643). In summary, this variant meets the criteria to be classified as pathogenic for mucopolysaccharidosis type 1. IDUA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases VCEP (Specifications Version 1.0.0): PM3_Very Strong, PM4, PP4, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 6, 2024)**

**Met criteria codes**

| | | |
|---|---|---|
| **PP4** | ✔ | At least twelve patients with a diagnosis of mucopolysaccharidosis type 1 have been reported in the literature, including four patients with documented laboratory values showing deficiency of IDUA activity in fibroblasts or leukocytes (PMID: 15300847, 21394825, 23786846) one of whom also had documented clinical features consistent with the diagnosis including corneal clouding, joint stiffness, digital contractures, cardiac valve disease, airway obstruction, and developmental delay (PMID: 15300847) (PP4). |
| **PM4** | ✔ | The NM_000203.5:c.c.46_57del variant in IDUA is predicted to cause a change in the length of the protein (p.Ser16_Ala19del) due to an in-frame deletion of 4 amino acids in a non-repeat region (PM4). |
| **PM3_Very Strong** | ✔ | Four patients have been reported who are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP including two confirmed in trans - c.1750C>T (p.Gln584Ter) (PMID: 12189649), 1 point; and p.Trp402Ter (PMID: 11735025), 1 point; and two phase unknown - c.208C>T (p.Gln70Ter) (PMID: 21394825), 0.5 points; and c.386-2A>G (PMID: 11735025), 0.5 points. In addition, at least two homozygotes have been reported PMID: 7951228, 21394825) (max 2 x 0.5 points). Total 4 points (PM3_VeryStrong). Additional patients are compound heterozygous for the variant and c.603C>G (p.Tyr201Ter) (PMID: 21394825), c.1189+5G>A (PMID: 21394825); c.1960T>C (p.Ter654ArgextTer*62) (PMID: 21394825), c.1049A>T (p.Asn350Ile) (PMID: 12559846) and c.1598C>G (p.Pro533Arg) (PMID: 15300847). The allelic data from these patients will be used in the classification of the second variant and is not included here to avoid circular logic. |
| **PM2_Supporting** | ✔ | The highest population minor allele frequency in gnomAD v4.1.0 is 0.00006251 (69/1103836 alleles) in the European non-Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). |

| | | | |
|---|---|---|---|
| **PS3_Supporting** | | ✔ | When expressed in COS-7 cells, the variant (labeled as "134del12") resulted in 124.6% of normal activity. A 77-kDa precursor protein was observed on Western blot, suggesting activity of precursor IDUA without posttranslational cleavage, compared with a major mature 63-kDa form and a minor 77-kDa precursor in cells transfected with wild-type cDNA (Fig. 2B). These results suggest that the variant prevents correct posttranslational processing and transport to the lysosome (PMID: 12189649). |

## Curation History

owing 1 to 1 of 1 rows

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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.