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Variant: NM_000203.5(IDUA):c.53T>C (p.Leu18Pro)

Version: 1.0

CA238566

193062 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1338850d-e7cf-4f83-85d0-f510c212432e
Approved on: 2025/5/19
Published on: 2025/5/22

HGVS expressions

NM_000203.5:c.53T>C
NM_000203.5(IDUA):c.53T>C (p.Leu18Pro)
NC_000004.12:g.987137T>C
CM000666.2:g.987137T>C
NC_000004.11:g.980925T>C
CM000666.1:g.980925T>C
NC_000004.10:g.970925T>C
NG_008103.1:g.5141T>C
NG_033042.1:g.11300A>G
ENST00000247933.9:c.53T>C
ENST00000514224.2:c.53T>C
ENST00000247933.8:c.53T>C
ENST00000398520.6:c.576+3991A>G
ENST00000502910.5:c.53T>C
ENST00000504568.5:c.51T>C
ENST00000506561.5:n.62T>C
ENST00000508168.5:n.72T>C
ENST00000514698.5:n.94T>C
ENST00000622731.4:c.576+3991A>G
NM_000203.4:c.53T>C
NM_134425.2:c.576+3991A>G
NR_110313.1:n.141T>C
NM_134425.3:c.576+3991A>G
NM_134425.4:c.576+3991A>G

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PP4_Moderate PM3_Strong

Not Met criteria codes 3

PP1 PP3 BP4

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.53T>C variant in IDUA is a missense variant predicted to cause substitution of Leucine by Proline at amino acid 18 (p.Leu18Pro). This variant has been detected in at least 10 individuals with MPS I. This variant has been detected in at least 10 individuals with MPS I. Of those individuals, three were homozygous for the variant (PMID 25256405, max 2 x 0.5 = 1 point). Four of the remaining individuals are compound heterozygous for this variant and a second variant that has been classified as pathogenic or likely pathogenic for MPS I by the ClinGen Lysosomal Diseases VCEP including c.1205G>A p.(Trp402Ter) (ClinVar Variation ID: 11908) (PMID 31194252, at least one patient, phase not confirmed, 0.5 point), c.208C>T p.(Gln70Ter) (ClinVar Variation ID: 11909) (PMID 31194252, 255574391 2 patients, phase not confirmed, 2 x 0.5 point), and c.1487C>G p.(Pro496Arg) (PMID 31194252, 1 patient, phase not confirmed, 0.25 point). Two patients are compound heterozygous for the variant and c.1163C>A, p.(Thr388Lys), however the allelic data for these patients will be used to support the classification of Thr388Lys and is not included here in order to avoid circular logic (2.75 points, PM3_strong). One patient with this variant present in the homozygous state has been reported with a clinical diagnosis of attenuated MPS1, presenting with reduced IDUA enzyme activity (0.73 nmol/h/mg, reference range 32-56) and increased GAG excretion in urine (188ug GAGs/g creatinine, age-related reference 67-124). His brother, also homozygous for the variant is reported to have attenuated MPS1, with similar clinical features (PMID 25256405) (PP4_moderate). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00002779 (1/35,980 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.319 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on IDUA function. There is a ClinVar entry for this variant (Variation ID: 193062). In summary, this variant meets the criteria to be classified as likely 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_strong, PP4_moderate, PM2_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 19, 2025).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00002779 (1/35,980 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).
PP4_Moderate	✔	One patient with this variant present in the homozygous state has been reported with a clinical diagnosis of attenuated MPSI, presenting with reduced IDUA enzyme activity (0.73 nmol/h/mg and 0.6nmol/h/mg, respectively, reference range 32-56) and increased GAG excretion in urine (188ug GAGs/g creatinine, age-related reference 67-124). His brother, also homozygous for the variant is also reported to have attenuated MPS I (PMID 25256405) (PP4_Moderate).
PM3_Strong	✔	This variant has been detected in at least 10 individuals with MPS I. Of those individuals, three were homozygous for the variant (PMID 25256405, max 2 x 0.5 = 1 point). Four of the remaining individuals are compound heterozygous for this variant and a second variant that has been classified as pathogenic or likely pathogenic for MPS I by the ClinGen Lysosomal Diseases VCEP including c.1205G>A p.(Trp402Ter) (ClinVar Variation ID: 11908) (PMID 31194252, at least one patient, phase not confirmed, 0.5 point), c.208C>T p.(Gln70Ter) (ClinVar Variation ID: 11909) (PMID 31194252, 255574391 2 patients, phase not confirmed, 2 x 0.5 point), and c.1487C>G p.(Pro496Arg) (PMID 31194252, 1 patient, phase not confirmed, 0.25 point). Two patients are compound heterozygous for the variant and c.1163C>A, p.(Thr388Lys), however the allelic data for these patients will be used to support the classification of Thr388Lys and is not included here in order to avoid circular logic (2.75 points, PM3_strong).

Not Met criteria codes

PP1	✖	One patient with this variant present in the homozygous state has been reported with a clinical diagnosis of attenuated MPS1, presenting with reduced IDUA enzyme activity (0.73 nmol/h/mg and 0.6nmol/h/mg, respectively, reference range 32-56) and increased GAG excretion in urine (188ug GAGs/g creatinine, age-related reference 67-124). His brother, also homozygous for the variant is also reported to have attenuated MPS1 (PMID 25256405). Discussed with experts and as parental segregation not confirmed, we cannot exclude possibility of a deletion and therefore not applying PP1.
PP3	✖	The computational predictor REVEL gives a score of 0.319 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on IDUA function.
BP4	✖	The computational predictor REVEL gives a score of 0.319 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on IDUA function.

Curation History

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