Variant: NM_000203.5(IDUA):c.1148G>A (p.Arg383His)

Version: 1.0

CA2802205

558189 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: 13e39906-5b23-4b69-b36d-9e16b8d522e3
Approved on: 2024-12-05
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HGVS expressions

NM_000203.5:c.1148G>A
NM_000203.5(IDUA):c.1148G>A (p.Arg383His)
NC_000004.12:g.1002444G>A
CM000666.2:g.1002444G>A
NC_000004.11:g.996232G>A
CM000666.1:g.996232G>A
NC_000004.10:g.986232G>A
NG_008103.1:g.20448G>A
ENST00000247933.9:c.1148G>A
ENST00000514224.2:c.1148G>A
ENST00000652070.1:n.1204G>A
ENST00000247933.8:c.1148G>A
ENST00000514224.1:c.752G>A
ENST00000514698.5:n.1255G>A
NM_000203.4:c.1148G>A
NR_110313.1:n.1236G>A
NM_001363576.1:c.752G>A

Pathogenic

Met criteria codes 6

PP1_Moderate PS3_Supporting PM3_Very Strong PP3_Moderate PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PM1

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.1148G>A variant in IDUA is a missense variant predicted to cause substitution of threonine by arginine at amino acid 383 (p.Arg383His). At least five patients with this variant had documented IDUA deficiency within the affected range in leukocytes, enzyme replacement therapy resulting in a significant reduction in total urine GAGs, and/or clinical features specific to MPS I including corneal and joint involvement (PMID: 23786846, 23837464, 31090850) (PP4_Moderate). This variant has been detected in at least 1 individual with MPS I who was homozygous for the variant (PMID: 7550242, 0.5 points). It has also been detected in at least 8 individuals who were compound heterozygous for the variant and a variant in IDUA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP; variants: c.208C>T (p.Gln70Ter) (ClinVar Variation ID: 11909)(PMID: 23837464, 0.5 points); c.266G>A (p.Arg89Gln) ((PMID: 31194252, 0.5 points), c.386-2A>G (ClinVar Variation ID: 222994) (PMID: 23837464, 2 unrelated patients, 2 x 0.5 points), c.266G>A (p.Arg89Gln) (ClinVar Variation ID: 11922) (PMID: 31194252, 0.5 points), c.979G>C (p.Ala327Pro) (Variation ID: 167190) (PMID: 12559846, 23837464, 0.5 points), c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (PMID: 12559846, 23837464, 0.5 points), c.1598C>G (p.Pro533Arg) (ClinVar Variation ID: 11910) (PMID: 30419879, 0.5 points); however, phase was not confirmed in any case (Total >4 points) (PM3_Very Strong). One pair of sibling with MPS I and compound heterozygous for the variant and p.Gln70Ter, and another pairs of siblings compound heterozygous for the variant and c.386-2A>G (aka c.474-2A>G) (PMID: 23837464) (PP1_Moderate). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001653 (14/84692 alleles) in the South Asian 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 activity of the variant was <2% wild type activity (PS3_Supporting). The computational predictor REVEL gives a score of 0.874 which is above the threshold of 0.773, evidence that correlates with impact to IDUA function at the moderate level based on the specifications of the ClinGen Lysosomal Diseases VCEP (PMID: 36413997) (PP3_Moderate). There is a ClinVar entry for the variant (Variation ID: 558189). 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 Diseases Variant Curation Expert panel (Specifications Version 1.0.0): PM3_Very Strong, PP1_Moderate, PP3_Moderate, PP4_Moderate, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 5, 2024)

Met criteria codes

PP1_Moderate	✔	One pair of sibling with MPS I and compound heterozygous for the variant and p.Gln70Ter, and another pairs of siblings compound heterozygous for the variant and c.386-2A>G (aka c.474-2A>G) (PMID: 23837464) (PP1_Moderate).
PS3_Supporting	✔	When expressed in CHO cells, the activity of the variant was <2% wild type activity (PS3_Supporting).
PM3_Very Strong	✔	This variant has been detected in at least 1 individual with MPS I who was homozygous for the variant (PMID: 7550242, 0.5 points). It has also been detected in at least 8 individuals who were compound heterozygous for the variant and a variant in IDUA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP; variants: c.208C>T (p.Gln70Ter) (ClinVar Variation ID: 11909)(PMID: 23837464, 0.5 points); c.266G>A (p.Arg89Gln) ((PMID: 31194252, 0.5 points), c.386-2A>G (ClinVar Variation ID: 222994) (PMID: 23837464, 2 unrelated patients, 2 x 0.5 points), c.266G>A (p.Arg89Gln) (ClinVar Variation ID: 11922) (PMID: 31194252, 0.5 points), c.979G>C (p.Ala327Pro) (Variation ID: 167190) (PMID: 12559846, 23837464, 0.5 points), c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (PMID: 12559846, 23837464, 0.5 points), c.1598C>G (p.Pro533Arg) (ClinVar Variation ID: 11910) (PMID: 30419879, 0.5 points); however, phase was not confirmed in any case (Total >4 points) (PM3_Very Strong).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.874 which is above the threshold of 0.773, evidence that correlates with impact to IDUA function at the moderate level based on the specifications of the ClinGen Lysosomal Diseases VCEP (PMID: 36413997) (PP3_Moderate).
PP4_Moderate	✔	At least five patients with this variant had documented IDUA deficiency within the affected range in leukocytes, enzyme replacement therapy resulting in a significant reduction in total urine GAGs, and/or clinical features specific to MPS I including corneal and joint involvement (PMID: 23786846, 23837464, 31090850) (PP4_Moderate).

PM2_Supporting	ℹ	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001653 (14/84692 alleles) in the South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.00025), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM1	ℹ	✖	Not located in hot spot or established functional domain.

Curation History

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