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Variant: NM_000203.5(IDUA):c.1598C>G (p.Pro533Arg)

Version: 1.0

CA256112

11910 (ClinVar)

Gene: IDUA (HGNC:3425)
Condition: mucopolysaccharidosis type 1 (MONDO:0001586)
Inheritance Mode: Autosomal recessive inheritance
UUID: a3a16dae-ae95-413e-9210-99a4f23d9b6e
Approved on: 2025/1/3
Published on: 2025/1/3

HGVS expressions

NM_000203.5:c.1598C>G
NM_000203.5(IDUA):c.1598C>G (p.Pro533Arg)
NC_000004.12:g.1003418C>G
CM000666.2:g.1003418C>G
NC_000004.11:g.997206C>G
CM000666.1:g.997206C>G
NC_000004.10:g.987206C>G
NG_008103.1:g.21422C>G
ENST00000247933.9:c.1598C>G
ENST00000514224.2:c.1598C>G
ENST00000652070.1:n.1654C>G
ENST00000247933.8:c.1598C>G
ENST00000514224.1:c.1202C>G
ENST00000514698.5:n.1705C>G
NM_000203.4:c.1598C>G
NR_110313.1:n.1686C>G
NM_001363576.1:c.1202C>G

Pathogenic

Met criteria codes 6

PP1_Moderate | PM3_Very Strong | PP3_Moderate | PP4_Moderate | 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.1598C>G variant in IDUA is a missense variant that is predicted to result in the substitution of proline by arginine at amino acid 533 (p.Pro533Arg). This variant is one of the more common variants identified in patients with mucopolysaccharidosis type 1 (MPS 1). The variant was found in 46 out of 538 patients in the International MPS 1 Registry (PMID: 31194252). It has been identified in patients with MPS 1 from different continents, and it is the most frequent variant in the north African countries (92% of MPS1 alleles in Morocco, 81% in Algeria, and 54% in Tunisia) (reviewed in PMID: 29393969). Of note, the severity of symptoms in individuals with this variant is variable; some homozygous individuals have severe disease while others have attenuated symptoms (PMID: 31194252). At least 50 patients with this variant have been reported including patients with documented laboratory values showing deficient iduronidase activity and detailed features consistent with MPS 1 such as dysmorphic facies, multiple dysostoses, joint stiffness, hepatomegaly, umbilical hernia, hearing loss, cardiovascular disease, and hydrocephalus and/or elevated urine GAGs (2 PP4 criteria met) (PMID: 10738517, 12796790, 1301941). One study provides details on the clinical features, IDUA activity, and GAG values for 9 patients (3 PP4 criteria met, PMID: 27196898) (PP4_Moderate). At least 24 individuals are homozygous for the variant (PMID: 1301941, 10738517, 12203999, 16435195, 24102521, 27196898, 28752568, 31194252, 31298590). At least 12 individuals are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, including at least 8 patients with c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (max 2 x 0.5 points), two patients with c.208C>T (p.Gln70Ter) (PMID: 31194252) (ClinVar Variation ID: 11909) (2 x 0.5 points), two apparently unrelated patients with c.1743C>G (p.Tyr581Ter) (ClinVar Variation ID: 550883) (2 x 0.5 points), and at least 24 homozygotes (max 2 x 0.5 points) (PMID: 31194252). 4 PM3 points (PM3_VeryStrong). Many additional individuals have been reported who are compound heterozygous for additional IDUA variants (PMID: 12203999, 12559846, 31194252). Additional evidence is available in the literature but the maximum points for PM3 have been reached (PM3_Very Strong). The variant has been shown to segregate with disease in families, including two families each with two affected children who are homozygous for the variant (PMID: 27196898) (PP1_Moderate). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0001975 (10/50624 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). Expression of the variant in CHO cells and tobacco BY-2 cells revealed that the protein is unstable, abnormally processed/trafficked, and has very low, but detectable (<1%), residual activity when compared to wild type (PMID: 12559846, 24036510) (PS3_Supporting). The computational predictor REVEL gives a score of 0.783 which is above the threshold of 0.773, evidence that correlates with impact to IDUA function at the moderate level (PP3_Moderate). No impact on splicing predicted by SpliceAI. There is a ClinVar entry for this variant (Variant ID: 11910). In summary, this variant meets the criteria to be classified as pathogenic for MPS 1. IDUA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases VCEP: 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 January 3, 2025)

Met criteria codes

PP1_Moderate	✔	Two families, each with two affected children who are homozygous for the variant (PMID: 27196898) (PP1_Moderate).
PM3_Very Strong	✔	At least 12 individuals are compound heterozygous for the variant and another variant in IDUA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, including at least 8 patients with c.1205G>A (p.Trp402Ter) (ClinVar Variation ID: 11908) (max 2 x 0.5 points), two patients with c.208C>T (p.Gln70Ter) (PMID: 31194252) (ClinVar Variation ID: 11909) (2 x 0.5 points), two apparently unrelated patients with c.1743C>G (p.Tyr581Ter) (ClinVar Variation ID: 550883) (2 x 0.5 points), and at least 24 homozygotes (max 2 x 0.5 points) (PMID: 31194252). 4 PM3 points (PM3_VeryStrong).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.783 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 (PP3_Moderate). No impact on splicing predicted by SpliceAI.
PP4_Moderate	✔	At least 50 patients with this variant have been reported including patients with documented laboratory values showing deficient iduronidase activity and detailed features consistent with MPS 1 such as dysmorphic facies, multiple dysostoses, joint stiffness, hepatomegaly, umbilical hernia, hearing loss, cardiovascular disease, and hydrocephalus and/or elevated urine GAGs (2 PP4 criteria met) (PMID: 10738517, 12796790, 1301941). One study

provides details on the clinical features, IDUA activity, and GAG values for 9 patients (3 PP4 criteria met, PMID: 27196898) (PP4_Moderate).

PM2_Supporting ✔ The highest population minor allele frequency in gnomAD v4.1.0. is 0.0001975 (10/50624 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).

PS3_Supporting ✔ Expression of the variant in CHO cells and tobacco BY-2 cells revealed that the protein is unstable, abnormally processed/trafficked, and has very low, but detectable (<1%), residual activity when compared to wild type (PMID: 12559846, 24036510) (PS3_Supporting).

Curation History

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