Variant: NM_000152.5(GAA):c.1441T>C (p.Trp481Arg)

Version: 1.0

CA274247

189007 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2f9f62d1-d280-478e-9aed-b8a1c5c4d838
Approved on: 2023-10-01
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HGVS expressions

NM_000152.5:c.1441T>C
NM_000152.5(GAA):c.1441T>C (p.Trp481Arg)
NC_000017.11:g.80110730T>C
CM000679.2:g.80110730T>C
NC_000017.10:g.78084529T>C
CM000679.1:g.78084529T>C
NC_000017.9:g.75699124T>C
NG_009822.1:g.14175T>C
ENST00000570803.6:c.1441T>C
ENST00000572080.2:c.1441T>C
ENST00000577106.6:c.1441T>C
ENST00000302262.8:c.1441T>C
ENST00000302262.7:c.1441T>C
ENST00000390015.7:c.1441T>C
NM_000152.3:c.1441T>C
NM_001079803.1:c.1441T>C
NM_001079804.1:c.1441T>C
NM_000152.4:c.1441T>C
NM_001079803.2:c.1441T>C
NM_001079804.2:c.1441T>C
NM_001079803.3:c.1441T>C
NM_001079804.3:c.1441T>C

Pathogenic

Met criteria codes 6

PS3_Supporting PM2_Supporting PP3 PP4_Moderate PM1 PM3_Strong

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1441T>C variant in GAA is predicted to result in the missense substitution of tryptophan by arginine at amino acid 481 (p.Trp481Arg). The variant has been reported in at least 6 individuals with Pompe disease in compound heterozygosity with another variant in GAA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP. It was confirmed in trans with c.1326+1G>A (PMIDs: 10189220, 9862843), and was found in unconfirmed phase with c.-32-13T>G (PMID: 14695532, 18757064, 22676651, 27189384, 29556838, 34357340); c.2560C>T (p.Arg854Ter) (PMIDs: 31086307, 35787971), c.1979G>A (p.Arg660His) (PMID: 31086307), and c.2481+102_c.2646+31del (PMID: 26497565, 28657663). Another patient is compound heterozygous for the variant and c.1556T>C (p.Met519Thr) (PMID: 31086307); the allelic data from this patient will be used in the assessment of the other variant and is not included here to avoid circular logic (PM3_Strong). This variant has been reported in individuals with specific phenotypic features of Pompe disease including documented laboratory values revealing GAA deficiency, individuals on enzyme replacement therapy, patients with documented symptoms of infantile onset Pompe disease, and elevated urine Hex4 (PMID: 26497565, 28657663, 31086307, 34357340) (PP4_Moderate). Trp481 is a residue that crystallography studies have shown to be important in the architecture of the active site and substrate binding of GAA; this residues has, therefore, has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (https://www.biorxiv.org/content/10.1101/212837v1.full.pdf, PMID: 29061980) (PM1). In two independent studies, expression of the variant in COS cells results in <2% GAA activity compared to normal, but also a significant amount of mature GAA protein, suggesting that the variant impacts catalysis rather than protein production or stability (PMID: 14695532, 19862843). The computational predictor REVEL gives a score of 0.967 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID:). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3_Strong, PM1, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting, (Classification approved by the ClinGen Lysosomal Diseases VCEP on Oct. 1, 2023)

Met criteria codes

PS3_Supporting	✔	In two independent studies, expression of the variant in COS cells results in <2% activity compared to normal, but also a significant amount of mature GAA protein, suggesting that the variants impacts catalysis rather than protein production or stability (PMID: 14695532, 19862843).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00008 (2/24904 alleles) in the African population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.967 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate	✔	This variant has been reported in individuals with specific phenotypic features of Pompe disease including documented laboratory values revealing GAA deficiency, individuals on enzyme replacement therapy, patients with documented symptoms of infantile onset Pompe disease, and elevated urine Hex4 (PMID: 26497565, 28657663, 31086307, 34357340) (PP4_Moderate).
PM1	✔	This variant alters amino acid Trp481, a residue that crystallography studies have shown to be important in the architecture of the active site and substrate binding of GAA; this residue has, therefore, been defined as a critical residue by the ClinGen LD VCEP (https://www.biorxiv.org/content/10.1101/212837v1.full.pdf, PMID: 29061980) (PM1).

PM3_Strong		✔	This variant has been reported in at least 6 individuals in compound heterozygosity with another variant in GAA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP including c.-32-13T>G (max 2 x 0.5 points; PMID: 14695532, 18757064, 22676651, 27189384, 29556838, 34357340); c.1326+1G>A, in trans, 1 point (PMIDs: 10189220, 9862843); c.2560C>T (p.Arg854Ter), phase unknown, 0.5 points (PMIDs: 31086307, 35787971), c.1979G>A (p.Arg660His), phase unknown, 0.5 points (PMID: 31086307), and c.2481+102_c.2646+31del, phase unknown, (PMID: 26497565, 28657663). Another patient is compound heterozygous for the variant and c.1556T>C (p.Met519Thr) (PMID: 31086307); the allelic data from this patient will be used in the assessment of the other variant and is not included here to avoid circular logic. Total 3.5 points (PM3_Strong).

Curation History

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