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Variant: NM_001079804.3:c.1400T>C

Version: 1.0

CA401366522

2840512 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 349e0b82-6338-4b3a-a5da-e902a32952d0
Approved on: 2024/1/16
Published on: 2024/3/26

HGVS expressions

NM_001079804.3:c.1400T>C
NC_000017.11:g.80110018T>C
CM000679.2:g.80110018T>C
NC_000017.10:g.78083817T>C
CM000679.1:g.78083817T>C
NC_000017.9:g.75698412T>C
NG_009822.1:g.13463T>C
ENST00000570803.6:c.1400T>C
ENST00000572080.2:c.1400T>C
ENST00000577106.6:c.1400T>C
ENST00000302262.8:c.1400T>C
ENST00000302262.7:c.1400T>C
ENST00000390015.7:c.1400T>C
NM_000152.3:c.1400T>C
NM_001079803.1:c.1400T>C
NM_001079804.1:c.1400T>C
NM_000152.4:c.1400T>C
NM_001079803.2:c.1400T>C
NM_001079804.2:c.1400T>C
NM_000152.5:c.1400T>C
NM_001079803.3:c.1400T>C

Likely Pathogenic

Met criteria codes 4

PM3 PM2_Supporting PP3 PP4_Moderate

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.1400T>C variant in GAA is predicted to result in the missense substitution of phenylalanine by serine at amino acid 467 (p.Phe467Ser). This variant has been detected in one patient with a diagnosis of infantile onset Pompe disease (IOPD) with documented deficient GAA activity and on enzyme replacement therapy (Clinical Diagnostic Laboratory) (PP4_Moderate). This variant was confirmed to be in trans with c.2560C>T (p.Arg854Ter), a GAA variant classified as pathogenic by the ClinGen LD VCEP (ClinVar Variation ID: 4034, SCV001371731.1), in one patient with IOPD (Clinical Diagnostic Laboratory) (PM3). The variant is absent in gnomAD v2.1.1. (PM2_Supporting). The computational meta-predictor REVEL has a score of 0.941 for the variant, which is above the threshold of 0.7, indicating a negative impact on GAA function (PP3). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen LD VCEP (Specifications Version 2.0): PM3, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen LD VCEP on Jan 16, 2024).

Met criteria codes

PM3	✔	This variant was confirmed (both parents being tested) to be in trans with c.2560C>T (p.Arg854Ter), a GAA variant classified as pathogenic by the ClinGen Lysosomal Diseases (LD) VCEP (ClinVar Variation ID: 4034, SCV001371731.1), in one patient with IOPD (Clinical Diagnostic Laboratory) (1.0 point; PM3).
PM2_Supporting	✔	Absent in gnomAD v2.1.1. and v4.0 (PM2_Supporting).
PP3	✔	The computational meta-predictor REVEL has a score of 0.941 for the variant, which is above the threshold of 0.7, indicating a negative impact on GAA function (PP3).
PP4_Moderate	✔	This variant has been detected in one patient with a diagnosis of infantile onset Pompe disease (IOPD) with documented deficient GAA activity and on enzyme replacement therapy (ERT) (Clinical Diagnostic Laboratory) (2 points; PP4_Moderate). The patient has biventricular concentric cardiac hypertrophy, positive newborn screen, abnormal urine Hex4 and positive CRIM status.

Curation History

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