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# *Variant: NM_000152.5(GAA):c.953T>C (p.Met318Thr)*

*CA116590*

*4021 (ClinVar)*

**Gene**: GAA (HGNC:2548)
**Condition**: glycogen storage disease II (MONDO:0009290)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** de2308b1-77ef-4469-911a-9ac15ea1b98b
**Approved on**: 2022-09-06
**Published on**: 2022-09-19

## *HGVS expressions*

**NM_000152.5(GAA):c.953T>C (p.Met318Thr)**
**NM_000152.5:c.953T>C**
NC_000017.11:g.80107894T>C
CM000679.2:g.80107894T>C
NC_000017.10:g.78081693T>C
CM000679.1:g.78081693T>C
NC_000017.9:g.75696288T>C
NG_009822.1:g.11339T>C
ENST00000302262.8:c.953T>C
ENST00000302262.7:c.953T>C
ENST00000390015.7:c.953T>C
NM_000152.3:c.953T>C
NM_001079803.1:c.953T>C
NM_001079804.1:c.953T>C
NM_000152.4:c.953T>C
NM_001079803.2:c.953T>C
NM_001079804.2:c.953T>C
NM_001079803.3:c.953T>C
NM_001079804.3:c.953T>C

**Pathogenic**

**Met criteria codes** 5

PS3_Supporting PP3 PM3_Very Strong PP4_Moderate PM2_Supporting

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Lysosomal Diseases VCEP***

**The NM_000152.5:c.953T>C variant in GAA is a missense variant predicted to cause substitution of methionine by threonine at amino acid 318 (p.Met318Thr). Twelve probands with a diagnosis of Pompe disease were identified with this variant. At least 9 of them have GAA activity in the affected range in dried blood spots or <30% normal GAA activity in fibroblasts (PMIDs: 1652892, 19862843, 25139343,**

**30214072, 34357340, clinical laboratory data) with pseudodeficiency variants confirmed absent in three of these patients (clinical laboratory data) (PP4_Moderate). Of these patients, 10 are compound heterozygous for c.953T>C (p.Met318Thr) and a variant in GAA that has been classified as pathogenic by the ClinGen LSD VCEP; either c.2560C>T (p.Arg854Ter), confirmed in trans (PMID: 1652892, 19862843), c.1979G>A (p.Arg660His), confirmed in trans by parental testing (clinical diagnostic laboratory); c.-32-13T>G, phase unknown (PMIDs: 29122469, 31904026, 32317649, clinical diagnostic laboratory) (at least 5 patients, 1 confirmed in trans) c.2481+102_2646+31del (p.Gly828_Asn882del), phase unknown (clinical diagnostic laboratory), c.1292_1295dupTGCA, phase unknown (PMID: 30214072), or c.1082C>T (p.Pro361Leu), phase unknown (PMID: 25139343). One patient is homozygous for the variant (PMID: 34357340) (0.5 points) (PM3_Very Strong). Another patient is compound heterozygous for the variant and c.692+5G>T (PMID: 29181627) but the allelic data from this patient will be used in the classification of c.692+5G>T and is not included here to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00009 in the African population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Suporting, and therefore meets this criterion (PM2_Supporting). Functional studies involving expression of the variant in cultured cells indicate that the variant impacts function, resulting in <2% GAA activity (PMID: 1652892, 19862843). The computational predictor REVEL gives a score of 0.89, 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: 4021; 1 star review status) with 3 submitters classifying the variant as pathogenic, two as likley pathogenic and one as a variant of uncertain significance. With data from the published literature and a clinical laboratory, we find that the variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG-AMP criteria met, as specified by the ClinGen LSD VCEP (Specifications Version 2.0): PM3_Very Strong, PP4_Moderate, PS3_Supporting, PM2_Supporting, PP3. Classification approved by the ClinGen LSD VCEP on Sept. 6, 2022.**

**Met criteria codes**

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|---|---|---|
| **PS3_Supporting** | ✔ | Functional studies involving expression of the variant in cultured cells indicate that the variant impacts function, resulting in <2% GAA activity (PMID: 1652892, 19862843). |
| **PP3** | ✔ | The computational predictor REVEL gives a score of 0.89, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). |
| **PM3_Very Strong** | ✔ | Twelve probands with a diagnosis of Pompe disease were identified with this variant. Of these patients, 10 are compound heterozygous for c.953T>C (p.Met318Thr) and a variant in GAA that has been classified as pathogenic by the ClinGen LSD VCEP; either c.2560C>T (p.Arg854Ter), confirmed in trans (PMID: 1652892, 19862843) (1 point), c.1979G>A (p.Arg660His), confirmed in trans by parental testing (clinical diagnostic laboratory) (1 point); c.-32-13T>G, phase unknown (PMIDs: 29122469, 31904026, 32317649, clinical diagnostic laboratory) (at least 5 patients, 1 confirmed in trans; maximum points 1 + 0.5 = 1.5); c.2481+102_2646+31del (p.Gly828_Asn882del), phase unknown (clinical diagnostic laboratory, 0.5 points); c.1292_1295dupTGCA, phase unknown (PMID: 30214072) (0.5 points), or c.1082C>T (p.Pro361Leu), phase unknown (PMID: 25139343) (0.5 points). One patient is homozygous for the variant (PMID: 34357340) (0.5 points). Another patient is compound heterozygous for the variant and c.692+5G>T (PMID: 29181627) but the allelic data from this patient will be used in the classification of c.692+5G>T and is not included here to avoid circular logic. Total points for PM3 = 6.5 points (PM3_Very Strong). |
| **PP4_Moderate** | ✔ | Twelve probands with a diagnosis of Pompe disease were identified with this variant. At least 9 of them have GAA deficiency shown by GAA activity in the affected range in dried blood spots or <30% normal GAA activity in fibroblasts (PMIDs: 1652892, 19862843, 25139343, 30214072, 34357340, clinical laboratory data) with pseudodeficiency variants confirmed absent in three of these patients and not reported in the others (clinical laboratory data) (PP4_Moderate). |
| **PM2_Supporting** | ✔ | The highest population minor allele frequency in gnomAD v2.1.1 is 0.00009 in the African population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Suporting, and therefore meets this criterion (PM2_Supporting). |

## Curation History

| See Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
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No matching records found