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# *Variant: NM_000152.4(GAA):c.2662G>T (p.Glu888Ter)*

Version: 1.0

*CA8815829*

*578595 (ClinVar)*

**Gene**: GAA (HGNC:2548)
**Condition**: glycogen storage disease II (MONDO:0009290)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 454d1ec5-7d41-447a-9045-ece71807477e
**Approved on**: 2020/5/4
**Published on**: 2020/5/27

## *HGVS expressions*

**NM_000152.4:c.2662G>T**
**NM_000152.4(GAA):c.2662G>T (p.Glu888Ter)**
NC_000017.11:g.80118668G>T
CM000679.2:g.80118668G>T
NC_000017.10:g.78092467G>T
CM000679.1:g.78092467G>T
NC_000017.9:g.75707062G>T
NG_009822.1:g.22113G>T
ENST00000570803.6:c.2662G>T
ENST00000572080.2:c.*800G>T
ENST00000577106.6:c.2662G>T
ENST00000302262.8:c.2662G>T
ENST00000302262.7:c.2662G>T
ENST00000390015.7:c.2662G>T
ENST00000573556.1:n.615G>T
NM_000152.3:c.2662G>T
NM_001079803.1:c.2662G>T
NM_001079804.1:c.2662G>T
NM_001079803.2:c.2662G>T
NM_001079804.2:c.2662G>T
NM_000152.5:c.2662G>T
NM_001079803.3:c.2662G>T
NM_001079804.3:c.2662G>T

**Pathogenic**

**Met criteria codes** 4

PP4 PM2 PVS1 PM3

Evidence Links 11

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

*Lysosomal Diseases VCEP*

**This variant, c.2662G>T (p.Glu888Ter), is a nonsense variant that is predicted to result in nonsense-mediated decay and lack of gene product, meeting PVS1. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00027 in the East Asian population, meeting PM2. At least 6 patients have been reported with this variant and deficiency of GAA activity meeting the ClinGen LSD VCEP's PP4 specifications. One of these individuals is compound heterozygous for the variant and c.-32-13T>G, phase unknown (PMID 16531044), and another is homozygous for the variant (PMID 17723315). This data meets PM3. Other individuals meeting PP4 specifications are compound heterozygous for the variant and either c.1574T>A (p.Phe525Tyr) (PMID 21232767), c.1935C>A (p.Asp645Glu) (PMID 18458862), or c.2238G>C (p.Trp746Cys) (PMID 25526786). However in each case, the in trans data from these patients will be used in the assessment of the other variant and was not used here in order to avoid a circular argument. Additional cases with the variant have been reported but were not included because the residual GAA activity was not provided, and therefore PP4 cannot be assessed (PMIDs 24269976, 25455803, 25626711, 27417441, 28394184, 31743840), or the patient carried a pseudodeficiency allele (PMID 21232767). There is a ClinVar entry for this variant (Variation ID: 578595) with two submitters classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PVS1, PM2, PM3, PP4.**

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**Met criteria codes**

**PP4** ✔

At least 6 patients have been reported with have been reported with this variant and GAA activity <10% normal in lymphocytes, leukocytes, or muscle samples, or <30% normal activity in cultured fibroblasts, or in the affected range in a GAA activity assay (PMIDs 16531044, 17723315, 18458862, 21232767, 25526786). This meets the specifications for PP4.

PubMed:25526786

**PM2** ✔

The highest population minor allele frequency in gnomAD v2.1.1 is 0.00027 (E. Asian) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.

**PVS1** ✔

This is a nonsense variant which is predicted to result in nonsense mediated decay and lack of gene product, meeting PVS1.

**PM3** ✔

At least 6 patients have been reported with this variant and deficiency of GAA activity meeting the ClinGen LSD VCEP's PP4 specifications. One of these individuals is compound heterozygous for the variant and c.-32-13T>G, phase unknown (PMID 16531044; 0.5 points), and another is homozygous for the variant (PMID 17723315; 0.5 points). A total of one point was given, meeting PM3. Other individuals meeting PP4 specifications are compound heterozygous for the variant and either c.1574T>A (p.Phe525Tyr) (PMID 21232767), c.1935C>A (p.Asp645Glu) (PMID 18458862), or c.2238G>C (p.Trp746Cys) (PMID 25526786). However in each case, the in trans data from these patients will be used in the assessment of the other variant and was not used here in order to avoid a circular argument. Additional cases with the variant have been reported but were not included because the residual GAA activity was not provided, and therefore PP4 cannot be assessed (PMIDs 24269976, 25455803, 25626711, 27417441, 28394184, 31743840), or the patient carried a pseudodeficiency allele (PMID 21232767).

PubMed:21232767
PubMed:31743840
PubMed:25455803
PubMed:17723315
PubMed:24269976
PubMed:18458862
PubMed:28394184

PubMed:27417441
PubMed:25626711
PubMed:16531044

## Curation History

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