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Variant: NM_000152.5(GAA):c.876C>G (p.Tyr292Ter)

Version: 2.0

CA401363871

637958 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 14fc9926-d268-4f0f-aab3-4067466438ad
Approved on: 2020/10/5
Published on: 2020/11/12

HGVS expressions

NM_000152.5(GAA):c.876C>G (p.Tyr292Ter)
NM_000152.5:c.876C>G
NC_000017.11:g.80107817C>G
CM000679.2:g.80107817C>G
NC_000017.10:g.78081616C>G
CM000679.1:g.78081616C>G
NC_000017.9:g.75696211C>G
NG_009822.1:g.11262C>G
ENST00000570803.6:c.876C>G
ENST00000572080.2:c.876C>G
ENST00000577106.6:c.876C>G
ENST00000302262.8:c.876C>G
ENST00000302262.7:c.876C>G
ENST00000390015.7:c.876C>G
NM_000152.3:c.876C>G
NM_001079803.1:c.876C>G
NM_001079804.1:c.876C>G
NM_000152.4:c.876C>G
NM_001079803.2:c.876C>G
NM_001079804.2:c.876C>G
NM_001079803.3:c.876C>G
NM_001079804.3:c.876C>G

Pathogenic

Met criteria codes 3
PM2 PVS1 PP4

Not Met criteria codes 1
PM3

Evidence Links 1

Expert Panel
Lysosomal Diseases VCEP

Criteria Specification Information
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.876C>G (p.Tyr292Ter), is a nonsense variant that is predicted to result in nonsense mediated decay and lack of gene product. Therefore, PVS1 can be applied. Functional studies, in which the variant was expressed in COS cells revealed no GAA activity in the cells or medium. However, a faint band representing GAA protein was detectable on Western blot (PMID 31510962). As the experiment was done in an in vitro expression system, it is unclear whether any gene product would be made in vivo. This variant was absent in gnomAD v2.1.1, meeting PM2. Two patients with infantile onset Pompe disease from Thailand have been reported (PMID 31510962). The residual GAA activity was provided for one of them, meeting PP4. This patient is compound heterozygous for the variant and c.1003G>A (p.Gly335Arg). The in trans data from this patient was used in the assessment of p.Gly335Arg and is not included here in order to avoid circular logic. The other patient is homozygous, and both parents were confirmed to be carriers, but the residual GAA activity is not available, and this data will not be included. Therefore, PM3 is currently not met. There is a ClinVar entry for this variant (Variation ID: 637958, 0 star review status) with one submitter (an author of this paper) 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, PP4.

Met criteria codes

PM2	✔	This variant is not in gnomAD v2.1.1.
PVS1	✔	This is a nonsense variant which is predicted to cause nonsense mediated decay resulting in no gene product. Therefore, PVS1 can be applied.
PP4	✔	Two patients with this variant have been reported. The residual GAA activity is available for one of them and meets the ClinGen LSD VCEP's specifications for PP4 (PMID 31510962).

Not Met criteria codes

PM3	✖	Two patients with this variant have been reported (PMID 31510962). Both of them have infantile onset Pompe disease. The residual GAA activity is reported for one of them, meeting PP4. This patient is compound heterozygous for the variant and c.1003G>A (p.Gly335Arg). The in trans data from this patient was used in the assessment of p.Gly335Arg and is not included here in order to avoid circular logic. The other patient is homozygous but PP4 is not met because the residual GAA activity was not reported. Therefore, PM3 is currently not met, based on the available data.

PubMed:31510962

Curation History

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