The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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: 2020-05-04
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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

PVS1 PP4 PM2 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.

Met criteria codes

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