

Variant: *NM_000152.5(GAA):c.2188G>T (p.Glu730Ter)*

Version: 1.2

CA401370663 [↗](#)

495665 (ClinVar) [↗](#)

Gene: GAA ([HGNC:2548](#))

Condition: glycogen storage disease II ([MONDO:0009290](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 33efa29d-6a70-4ac2-92cd-e08412f00686

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HGVS expressions

NM_000152.5:c.2188G>T

NM_000152.5(GAA):c.2188G>T (p.Glu730Ter)

NC_000017.11:g.80113365G>T

CM000679.2:g.80113365G>T

NC_000017.10:g.78087164G>T

CM000679.1:g.78087164G>T

NC_000017.9:g.75701759G>T

NG_009822.1:g.16810G>T

ENST00000570803.6:c.2188G>T

ENST00000572080.2:c.*326G>T

ENST00000577106.6:c.2188G>T

ENST00000302262.8:c.2188G>T

ENST00000302262.7:c.2188G>T

ENST00000390015.7:c.2188G>T

ENST00000572080.1:c.607G>T

NM_000152.3:c.2188G>T

NM_001079803.1:c.2188G>T

NM_001079804.1:c.2188G>T

NM_000152.4:c.2188G>T

NM_001079803.2:c.2188G>T

NM_001079804.2:c.2188G>T

NM_001079803.3:c.2188G>T

NM_001079804.3:c.2188G>T

Pathogenic

Met criteria codes **4**

PP4 PM3 PM2 PVS1

Evidence Links **0**

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.2188G>T (p.Glu730Ter), is a nonsense variant that is predicted to result in nonsense-mediated decay and lack of gene product. This is supported by functional studies in HEK293T cells and COS-1 cells, which showed undetectable GAA activity (PMIDs 12923862, 21972175). This variant is absent in gnomAD v2.1.1. It has been reported in 3 patients with Pompe disease who meet the ClinGen LSD VCEP specifications for PP4; two are compound heterozygous for the variant and c.-31-13T>G (PMIDs 28196920, 28951071; phase unknown) and one is compound heterozygous for the variant and a frameshift variant, c.829_851del, confirmed in trans (PMID 12923862), meeting PM3. There is a ClinVar entry for this variant (Variation ID: 495665, one star review status) with one submitter 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

PP4			Three individuals have been reported with this variant and GAA activity <10% normal in lymphocytes or leukocytes or in the affected range when compared to the laboratory's control range.
PM3			This variant was found in compound heterozygosity with a unique pathogenic variant in GAA in 2 patients with Pompe disease who also meet the ClinGen LSD VCEP's PP4. The phase of the variants is unknown in one case (PMID 28196920) and confirmed in the second case (PMID 12923862). Additional cases were reported but not included because a case with the same variant (not confirmed in trans) had already been included (PMID 28951071). Based on the ClinGen LSD VCEP's specifications, this data was given a total of 1.5 points which meets PM3.
PM2			This variant is absent 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.

Curation History

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