

Variant: NM_000152.5(GAA):c.2297A>G (p.Tyr766Cys)

Version: 1.0

CA8815679 [↗](#)

285197 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: d4761c6e-1e21-4164-8b4e-19cc8309700c

Approved on: 2024/6/6

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HGVS expressions

NM_000152.5:c.2297A>G

NM_000152.5(GAA):c.2297A>G (p.Tyr766Cys)

NC_000017.11:g.80117075A>G

CM000679.2:g.80117075A>G

NC_000017.10:g.78090874A>G

CM000679.1:g.78090874A>G

NC_000017.9:g.75705469A>G

NG_009822.1:g.20520A>G

ENST00000570803.6:c.2297A>G

ENST00000572080.2:c.*435A>G

ENST00000577106.6:c.2297A>G

ENST00000302262.8:c.2297A>G

ENST00000302262.7:c.2297A>G

ENST00000390015.7:c.2297A>G

ENST00000572080.1:c.716A>G

ENST00000573556.1:n.250A>G

NM_000152.3:c.2297A>G

NM_001079803.1:c.2297A>G

NM_001079804.1:c.2297A>G

NM_000152.4:c.2297A>G

NM_001079803.2:c.2297A>G

NM_001079804.2:c.2297A>G

NM_001079803.3:c.2297A>G

NM_001079804.3:c.2297A>G

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP3

PP4_Moderate

PM5

PM3_Strong

Not Met criteria codes **1**

PM1

Evidence Links **0**

Expert Panel

[Lysosomal Diseases VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2

[↗](#) **PDF**

[↗](#) **Criteria Specification Approval History**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.2297A>G variant in GAA is predicted to result in the substitution of tyrosine by cysteine at amino acid 766 (p.Tyr766Cys). At least five patients diagnosed with Pompe disease, all late onset symptoms, have been reported with this variant. Three of these patients have documented laboratory values showing deficiency GAA activity (PMID: 29124014, 35071497, 37087815) (PP4_Moderate). Four patients are compound heterozygous for the variant and another variant that has been classified as pathogenic by the ClinGen LD VCEP, all phase unconfirmed, including c.2481+110_2646+39del (ClinVar Variation ID: 657307) (PMID: 37087815, 0.5 points), c.784G>A (p.Glu262Lys) (ClinVar Variation ID: 188806, SCV002032128.1) (PMID: 35071497, 0.5 points), c.2560C>T (p.Arg854Ter) (ClinVar Variation ID: 4034, SCV001371731.1) (PMID: 30564623, 0.5 points), and c.1309C>T (p.Arg437Cys) (ClinVar Variation ID: 189082, SCV002540662.1) (PMID: 29124014, 0.5 points). Total 2 points (PM3_Strong). Another patient is reported with variant c.2297A>G (p.Tyr765Cys), which presumably is a typo for the amino acid number but cannot be confirmed (PMIDs: 21605996, 22676651). Another individual was identified by newborn screen, compound heterozygous for c.-32-13T>G (PMID: 33073003) but is not yet symptomatic, so was not included. One patient is compound heterozygous for the variant and c.1879_1881delTCC (p.Ser627del) ((PMID: 35071497), The allelic data from this patient will be used in the assessment of p.Ser627del and is not included here to avoid circular logic. The highest population minor allele frequency (MAF) in gnomAD v2.1.1 is 0.00006534 (2/30610 alleles) in the South Asian population. In gnomAD v4.1, the highest MAF is 0.00002227 (1/44894 alleles) in the East Asian population. Both are lower than the ClinGen LD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.967 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another amino acid change at the same position, c.2297A>C (p.Tyr766Ser)(ClinVar Variation ID: 420102), has been classified as pathogenic based on the specifications of the ClinGen LD VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 285197). 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 Lysosomal Diseases VCEP (Specifications Version 2.0): PM3_Strong, PM5, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on June 6, 2024)

Met criteria codes

PM2_Supporting		The highest population minor allele frequency (MAF) in gnomAD v2.1.1 is 0.00006534 (2/30610 alleles) in the South Asian population. In gnomAD v4.1, the highest MAF is 0.00002227 (1/44894 alleles) in the East Asian population. Both are lower than the ClinGen LD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP3	 	The computational predictor REVEL gives a score of 0.967 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate	 	At least five patients diagnosed with Pompe disease, all late onset symptoms, have been reported with this variant. Three of these patients have documented laboratory values showing deficiency GAA activity (PMID: 29124014, 35071497, 37087815) (PP4_Moderate).
PM5	 	Another amino acid change at the same position, c.2297A>C (p.Tyr766Ser)(ClinVar Variation ID: 420102), has been classified as pathogenic based on the specifications of the ClinGen LD VCEP (PM5).
PM3_Strong	 	Four patients are compound heterozygous for the variant and another variant that has been classified as pathogenic by the ClinGen LD VCEP, all phase unconfirmed, including c.2481+110_2646+39del (ClinVar Variation ID: 657307) (PMID: 37087815, 0.5 points), c.784G>A (p.Glu262Lys) (ClinVar Variation ID: 188806, SCV002032128.1) (PMID:

35071497, 0.5 points), c.2560C>T (p.Arg854Ter) (ClinVar Variation ID: 4034, SCV001371731.1) (PMID: 30564623, 0.5 points), and c.1309C>T (p.Arg437Cys) (ClinVar Variation ID: 189082, SCV002540662.1) (PMID: 29124014, 0.5 points). Total 2 points (PM3_Strong). Another patient is reported with variant c.2297A>G (p.Tyr765Cys), which presumably is a typo for the amino acid number but cannot be confirmed (PMIDs: 21605996, 22676651). Another individual was identified by newborn screen, compound heterozygous for c.-32-13T>G (PMID: 33073003) but is not yet symptomatic, so was not included. One patient is compound heterozygous for the variant and c.1879_1881delTCC (p.Ser627del) ((PMID: 35071497), The allelic data from this patient will be used in the assessment of p.Ser627del and is not included here to avoid circular logic.

Not Met criteria codes

PM1

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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