

Variant: *NM_000152.5(GAA):c.1735G>A (p.Glu579Lys)*

Version: 1.0

CA294895841 [↗](#)

495664 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 751727f5-33d5-4e67-a898-c4ef9dba3fcc

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HGVS expressions

NM_000152.5:c.1735G>A

NM_000152.5(GAA):c.1735G>A (p.Glu579Lys)

NC_000017.11:g.80112081G>A

CM000679.2:g.80112081G>A

NC_000017.10:g.78085880G>A

CM000679.1:g.78085880G>A

NC_000017.9:g.75700475G>A

NG_009822.1:g.15526G>A

ENST00000570803.6:c.1735G>A

ENST00000572080.2:c.1735G>A

ENST00000577106.6:c.1735G>A

ENST00000302262.8:c.1735G>A

ENST00000302262.7:c.1735G>A

ENST00000390015.7:c.1735G>A

ENST00000572080.1:c.123G>A

ENST00000572803.1:n.349G>A

NM_000152.3:c.1735G>A

NM_001079803.1:c.1735G>A

NM_001079804.1:c.1735G>A

NM_000152.4:c.1735G>A

NM_001079803.2:c.1735G>A

NM_001079804.2:c.1735G>A

NM_001079803.3:c.1735G>A

NM_001079804.3:c.1735G>A

Pathogenic

Met criteria codes **5**

PS3_Moderate **PM3_Strong**

PM2_Supporting **PP3**

PP4_Moderate

Evidence Links **1**

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Lysosomal Diseases VCEP

The NM_000152.:c.1735G>A variant in GAA is a missense variant predicted to result in the substitution of glutamate by lysine at amino acid 579 (p.Glu579Lys). Five patients with a diagnosis of Pompe disease and the variant have been reported, three with documented laboratory values showing deficiency of GAA activity (PMID: 21676566, 23601496, 29124014, 34357340), one with reported features consistent with infantile-onset Pompe disease (PMID: 24269976), and another reported to have Pompe disease (PMID: 14695532) (PP4_Moderate). Four of these patients are compound heterozygous for the variant and a variant in GAA that has been classified as pathogenic by the ClinGen LSD VCEP, all phase unknown, including c.-32-13T>G (PMID: 34357340) (0.5 points), c.525delT (PMID: 14695532) (0.5 points), c.2237G>A (p.Trp746Ter) (PMID: 24269976) (0.5 points), and c.655G>A (p.Gly219Arg) (PMIDs: 23601496, 31086307,31193175) (0.5 points). Total 2 points (PM3_Strong). Another patient is compound heterozygous for the variant and c.1857C>G (p.Ser619Arg) (PMIDs: 21676566, 29124014) The allelic data from this patient will be used in the classification of p.Ser619Arg and is not included here to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 (2/129092) in the European Non-Finnish population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). When expressed in COS cells, this variant had <5% GAA activity in cells and <2% in medium, evidence of abnormal synthesis and processing on Western blot, and did not localize to the lysosomes (PMID: 14695532, 19862843) (PS3_Moderate). The computational predictor REVEL gives a score of 0.878 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 495664). In summary this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG-AMP criteria met, as specified by the Clingen Lysosomal Storage Disorders VCEP (Specifications Version 2.0): PM3_Strong, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen LSD VCEP on December 6, 2022)

Met criteria codes

PS3_Moderate			When expressed in COS cells, this variant had <5% GAA activity in cells and <2% in medium, evidence of abnormal synthesis and processing on Western blot, and did not localize to the lysosomes (PMID: 14695532, 19862843) (PS3_Moderate).
			The variant was introduced into GAA cDNA by site directed mutagenesis and subcloned into a plasmid vector. The integrity of the insert was verified by sequencing. COS cells transfected with the variant had GAA activity of 3.8 +/-0.3 % of normal (3 replicates). Controls used included mock transfected cells (negative control) and wild type cDNA (positive control). The variant did not localize to the lysosomes, as demonstrated by lack of overlap in GAA and LAMP2 (lysosomal marker) immunolocalization. 1-Deoxynojirimycin, a molecular chaperone, resulted in a 3.5 fold increase in activity and lysosomal localization of the variant. PubMed:19862843 
PM3_Strong			Four patients are compound heterozygous for the variant and a variant in GAA that has been classified as pathogenic by the ClinGen LSD VCEP, all phase unknown, including c.-32-13T>G (PMID: 34357340) (0.5 points), c.525delT (PMID: 14695532) (0.5 points), c.2237G>A (p.Trp746Ter) (PMID: 24269976) (0.5 points), and c.655G>A (p.Gly219Arg) (PMID: 23601496, 31086307, 31193175) (0.5 points). Total 2 points (PM3_Strong). Another patient is compound heterozygous for the variant and c.1857C>G (p.Ser619Arg) (PMIDs: 21676566, 29124014) The allelic data from this patient will be used in the classification of p.Ser619Arg and is not included here to avoid circular logic.
PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 (2/129092) in the European Non-Finnish population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion.
PP3			The computational predictor REVEL gives a score of 0.878 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). SpliceAI predicts no impact on splicing.
PP4_Moderate			Five patients with a diagnosis of Pompe disease and the variant have been reported, three with documented laboratory values showing deficiency of GAA activity (PMID: 21676566, 23601496, 29124014, 34357340) (2 points

each, meeting PP4_Moderate), one with reported features consistent with infantile-onset Pompe disease (PMID: 24269976) (1 point, PP4), in addition to another reported patient with insufficient detail to apply PP4 (PMID: 14695532).

Curation History

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