

Variant: *NM_000152.5(GAA):c.784G>A (p.Glu262Lys)*

Version: 1.0

CA273984 [↗](#)

188806 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: b5e75561-1400-4069-9027-2a7c802ad249

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HGVS expressions

NM_000152.5:c.784G>A

NM_000152.5(GAA):c.784G>A (p.Glu262Lys)

NC_000017.11:g.80107648G>A

CM000679.2:g.80107648G>A

NC_000017.10:g.78081447G>A

CM000679.1:g.78081447G>A

NC_000017.9:g.75696042G>A

NG_009822.1:g.11093G>A

ENST00000570803.6:c.784G>A

ENST00000572080.2:c.784G>A

ENST00000577106.6:c.784G>A

ENST00000302262.8:c.784G>A

ENST00000302262.7:c.784G>A

ENST00000390015.7:c.784G>A

ENST00000570803.5:c.784G>A

NM_000152.3:c.784G>A

NM_001079803.1:c.784G>A

NM_001079804.1:c.784G>A

NM_000152.4:c.784G>A

NM_001079803.2:c.784G>A

NM_001079804.2:c.784G>A

NM_001079803.3:c.784G>A

NM_001079804.3:c.784G>A

Pathogenic

Met criteria codes **4**

PM3_Very Strong

PP3

PM2_Supporting

PP4_Moderate

Not Met criteria codes **1**

PM5

Evidence Links **0**

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

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

Lysosomal Diseases VCEP

This variant, NM_000152.5(GAA):c.784G>A, is predicted to result in the substitution of glutamate to lysine at amino acid 262 (p.Glu262Lys). This variant represented 6.8% of alleles in an Italian case series of 29 infants with Pompe disease (PMID: 18429042). This variant has been reported in at least 20 individuals with Pompe disease, including at least 12 individuals with documented laboratory data showing deficiency of GAA activity and/or clinical symptoms consistent with infantile onset Pompe disease (cardiomegaly and muscle weakness), and/or on treated with enzyme replacement therapy (ERT) meeting the ClinGen LSD VCEP’s specifications for PP4_Moderate (PMID 11738358, 18285536, 19588081, 19948615, 25455803, 26497565, 27344650, 29181627, 29422078, 30023291, 31193175 31915562, 33228748)(PP4_Moderate). The variant has been reported in compound heterozygosity with a pathogenic variant in at least 8 patients, phase unconfirmed (PMID: 11738358, 18285536, 19948615, 24269976, 25455803, 29181627, 29422078, 29880332), and in at least 5 homozygous patients diagnosed with Pompe disease (PMIDs: 18429042, 26497565, 29422078, 33228748, 33325062) (PM3_Very Strong). More data is available in the literature but the maximum evidence for PM3_Very Strong has been reached. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, allowing this criterion to be applied (PM2_Supporting). The computational predictor REVEL gives a score of 0.888 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). To our knowledge, the results of functional studies have not been reported for this variant. There is a ClinVar entry for this variant (ClinVar variation ID: 188806) with 3 submitters classifying the variant as pathogenic and two as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen LSD VCEP (Specification Version 2.0): PM3_Very Strong, PP4_Moderate, PP3, PM2_Supporting. (Classification approved: August 17, 2021)

Met criteria codes

PM3_Very Strong			The variant has been reported in compound heterozygosity in patients diagnosed with Pompe disease along with the following variants which are pathogenic based on classification by the ClinGen LSD VCEP: c.655G>A (p.Gly219Arg) (PMID: 11738358; 0.5 points), c.1396delG (PMID: 18285536, 0.5 points), c.1935C>A (p.Asp645Glu) (PMID: 19948615; 0.5 points), c.1356delC (PMID: 24269976; 0.5 points), c.1933G>A (p.Asp645Asn) (PMID: 25455803; 0.5 points), c.1822C>T (p.Arg608Ter) (PMID: 29422078, 0.5 points), c.-32-13T>G (PMID: 29880332; 2 patients; 2 x 0.5 points), and well as in patients who are homozygous for the variant (PMID: 18429042, 26497565, 29422078, 33228748, 33325062; max 1 point). The total, >4 points, meets PM3_Very Strong.
PP3			The computational predictor REVEL gives a score of 0.888 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, allowing this criterion to be applied.
PP4_Moderate			This variant has been reported in at least 20 individuals with Pompe disease, including at least 9 individuals with documented laboratory data showing deficiency of GAA activity and/or clinical symptoms consistent with infantile onset Pompe disease (cardiomegaly and muscle weakness), and/or on treated with enzyme replacement therapy (ERT) meeting the ClinGen LSD VCEP’s specifications for PP4_Moderate (PMID 11738358, 18285536,19948615, 26497565, 27344650, 29181627, 29422078, 31915562, 33228748), at least 4 patients with deficiency of GAA activity, or clinical symptoms consistent with infantile onset Pompe disease, or on ERT meeting PP4 (PMIDs 19588081, 25455803, 30023291, 31193175), with additional patients also reported to have Pompe disease (PMID 18429042, 22980766, 24269976, 29122469, 29880332 (PP4_Moderate).

Not Met criteria codes

PM5		
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Another amino acid change at the same codon, c.784G>C (p.Glu262Gln), has been reported. This variant has not yet been classified. The data will be used for the evaluation of p.Glu262Gln and, therefore, PM5 was not applied here in order to avoid circular logic.

Curation History

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