Variant: NM_000152.5(GAA):c.1317GAT[1] (p.Met440del)

Version: 2.0

CA658795250

526518 (ClinVar)

Gene: GAA
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: a98b509a-813f-4fa4-a2b8-d777c8deae09
Approved on: 2025-10-08
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HGVS expressions

NM_000152.5:c.1317GAT[1]
NM_000152.5:c.1320_1322delGAT
NM_000152.5(GAA):c.1317GAT[1] (p.Met440del)
NC_000017.11:g.80108822_80108824del
CM000679.2:g.80108822_80108824del
NC_000017.10:g.78082621_78082623del
CM000679.1:g.78082621_78082623del
NC_000017.9:g.75697216_75697218del
NG_009822.1:g.12267_12269del
ENST00000570803.6:c.1320_1322del
ENST00000572080.2:c.1320_1322del
ENST00000577106.6:c.1320_1322del
ENST00000302262.8:c.1320_1322del
ENST00000302262.7:c.1320_1322del
ENST00000390015.7:c.1320_1322del
NM_000152.3:c.1320_1322del
NM_001079803.1:c.1320_1322del
NM_001079804.1:c.1320_1322del
NM_000152.4:c.1320_1322del
NM_001079803.2:c.1320_1322del
NM_001079804.2:c.1320_1322del
NM_000152.5:c.1320_1322del
NM_001079803.3:c.1320_1322del
NM_001079804.3:c.1320_1322del

Likely Pathogenic

Met criteria codes 4

PM3 PM4_Supporting PP4_Moderate PM2_Supporting

Not Met criteria codes 2

PP3 PS3

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

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5: c.1320_1322delGAT variant is predicted to cause a change in the length of protein due to an in-frame deletion of one amino acid Met440 in a non-repeat region (PM4_Supporting). This variant has been detected in at least 3 individuals with Pompe disease. All of them were compound heterozygous for the variant and a pathogenic variant (2 cases with c.2238G>C p.Trp746Cys PMIDs: 25526786, 35071497; 1 case with c.2560C>T p.Arg854Ter PMID 28394184. 1.5 total points), meeting PM3. At least 2 patients with this variant had been reported as LOPD, one with documented GAA deficiency with <10% of normal mean control level of GAA activity (PMID: 35071497), one with muscle weakness and need ventilator support (PMID: 25526786), and another patient with this variant had been reported as IOPD (PMID: 28394184) (PP4_moderate). The variant is absent in gnomAD v4.1.0 (PM2_supporting). There is a ClinVar entry for this variant (Variant ID: 526518). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0). Criteria applied: PM2_supporting; PM3, PM4_supporting, PP4_moderate. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on August 8, 2025)

Met criteria codes

PM3	✔	This variant has been detected in at least 3 individuals with Pompe disease. All of them were compound heterozygous for the variant and a pathogenic variant (2 cases with c.2238G>C p.Trp746Cys PMIDs: 25526786, 35071497; 1 case with c.2560C>T p.Arg854Ter PMID 28394184. 1.5 total points). PM3 met.
PM4_Supporting	✔	The NM_000152.5: c.1320_1322del is predicted to cause a change in the length of protein due to an i-frame deletion of one amino acid Met440 in a non-repeat region (PM4_Supporting).
PP4_Moderate	✔	At least 2 patients with this variant had been reported as LOPD, one with documented GAA deficiency with <10% of normal mean control level of GAA activity (PMID: 35071497), one with muscle weakness and need ventilator support (PMID: 25526786). Another patient with this variant had been reported as IOPD (PMID: 28394184). Meets PP4_moderate.
PM2_Supporting	✔	GAA c.1317GAT[1] (p.Met440del) is absent at gnomAD.

Not Met criteria codes

PP3	✖	MutationTaster scored it as benign, and MutPredIndel is right at 0.5 which is deleterious with a 10% false positive rate. Due to conflicting in silico predictions, neither PP3 nor BP4 is met.
PS3	✖	To our knowledge, there is no published functional data for the variant.

Curation History

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