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# *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**: 2025/10/8
**Published on**: 2025/10/28

## *HGVS expressions*

**NM_000152.5(GAA):c.1317GAT[1] (p.Met440del)**
**NM_000152.5:c.1317GAT[1]**
**NM_000152.5:c.1320_1322delGAT**
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

PM4_Supporting PP4_Moderate PM2_Supporting PM3

**Not Met criteria codes** 2

PS3 PP3

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**

| | | |
|---|---|---|
| **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. |
| **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. |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PS3** | ✖ | To our knowledge, there is no published functional data for the variant. |
| **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. |

Curation History

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