

Variant: *NM_000152.5:c.1962_1964del*

Version: 1.0

CA294896907 [↗](#)

932896 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 10e16111-a4ca-4f6d-9251-2d3539039820

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HGVS expressions

NM_000152.5:c.1962_1964del

NC_000017.11:g.80112949_80112951del

CM000679.2:g.80112949_80112951del

NC_000017.10:g.78086748_78086750del

CM000679.1:g.78086748_78086750del

NC_000017.9:g.75701343_75701345del

NG_009822.1:g.16394_16396del

ENST00000570803.6:c.1962_1964del

ENST00000572080.2:c.*100_*102del

ENST00000577106.6:c.1962_1964del

ENST00000302262.8:c.1962_1964del

ENST00000302262.7:c.1962_1964del

ENST00000390015.7:c.1962_1964del

ENST00000570716.1:n.402_404del

ENST00000572080.1:c.381_383del

NM_000152.3:c.1962_1964del

NM_001079803.1:c.1962_1964del

NM_001079804.1:c.1962_1964del

NM_000152.4:c.1962_1964del

NM_001079803.2:c.1962_1964del

NM_001079804.2:c.1962_1964del

NM_001079803.3:c.1962_1964del

NM_001079804.3:c.1962_1964del

Pathogenic

Met criteria codes **6**

PS3

PM4_Supporting

PP3

PP4

PM2

PM3

Evidence Links **3**

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.1962_1964delAGA, is predicted to result in an inframe deletion of one amino acid in GAA, p.Glu656del, meeting PM4_Supporting. This variant is not present in gnomAD v2.1.1, meeting PM2. From unpublished clinical laboratory data, three patients with this variant meet the ClinGen LSD VCEP’s specifications for PP4. One of these individuals is homozygous for the variant and the parents are confirmed to be heterozygous; one individual is compound heterozygous for the variant and c.2237G>A (p.Trp746Ter); and one individual is compound heterozygous for the variant and c.883C>A (p.His295Asn). Based on this data, PM3 is met. At least one Indian patient with this variant has been described but full details, such as reference range for GAA activity, were not provided and therefore the data was not included (PMIDs 22711147, 22791670). When expressed in COS-7 cells, the variant has 2% wild type GAA activity and exhibits abnormal GAA processing on Western blot (PMID 18425781), meeting PS3. PROVEAN and Mutation Taster predict that the variant has a deleterious impact on protein function, meeting PP3. There is no ClinVar entry for this variant. In summary, this variant meets the criteria to be classified as a pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, based on the specifications of the ClinGen LSD VCEP: PS3, PM2, PM3, PM4_Supporting, PP3, PP4.

Met criteria codes		
PS3	 	<p>This variant results in 2% GAA activity and abnormal GAA processing when expressed in COS-7 cells, and was classified as Class B ("potentially less severe") by Kroos et al, 2008 (PMID 18425781), meeting the ClinGen LSD VCEP criteria for PS3.</p> <hr/> <p>Transient expression of this variant in COS-7 cells resulted in low GAA activity (2% of wild type activity in cells, and 0% in the medium). Western blot revealed abnormal GAA processing with reduced levels of the active 76 kDa species in cells and medium. The variant was classified as Class B (“potentially less severe”). PubMed:18425781 </p>
PM4_Supporting	 	<p>This variant results in an inframe single amino acid deletion (p.Glu655del) in GAA, meeting the ClinGen LSD VCEP criteria for PM4_Supporting.</p>
PP3	 	<p>Multiple lines of computational evidence predict that this variant is deleterious. The PROVEAN score is -12.376 (meeting the threshold of -2.5 for deleterious), and Mutation Taster predicts that this variant is "disease causing".</p>
PP4	 	<p>This variant was reported in a study of Indian patients with Pompe disease (PMID 22791670). While the authors report the GAA activity in these patients, the data cannot be included because the reference range was not provided. From unpublished clinical laboratory data, 3 patients have with GAA activity in the affected range in dried blood spots, meeting PP4.</p> <hr/> <p>In a study of Indian patients with suspected lysosomal storage disorders, 3 patients were identified with variants in GAA, at least one of whom had this variant and p.Asp489Asn (from the data, it is not clear if one or two patients have this genotype). The range of GAA activity, measured in skin fibroblasts, for these patients is 2.4-5.6 nmol/h/mg. However, because the reference range not provided in the paper, this data cannot be included. PubMed:22791670 </p>
PM2	 	<p>The highest population minor allele frequency in gnomAD v2.1.1 is 0.0000489 in the Finnish population. This variant is not present in any other population in gnomAD v2.1.1, meeting PM2.</p>
PM3	 	<p>From unpublished clinical laboratory data, 3 patients have with GAA activity meeting PP4. One of these individuals is homozygous for the variant and the parents are confirmed to be heterozygous (0.5 points), one is compound heterozygous for the variant and c.2237G>A (p.Trp746Ter), which is pathogenic based on assessment by the ClinGen LSD VCEP) (0.5 points), and one is compound heterozygous for the variant and c.883C>A (p.His295Asn).</p>

Based on this data, 1 point was given, meeting PM3. At least one patient has been described with this variant in the literature but were not included because PP4 was not met (PMIDs 22711147, 22791670).

A patient is described who is compound heterozygous for p.Gln355del and p.Asp489Asn (from the data, it is not clear if one or two patients have this genotype). The range of GAA activity, measured in skin fibroblasts, for these patients is 2.4-5.6 nmol/h/mg; reference range not provided. p.Asp489Asn has multiple submitters in ClinVar and is classified as pathogenic/likely pathogenic. [PubMed:22791670](#)

The paper describes an Indian family with a previously child affected by infantile onset Pompe disease who passed away. No genetic testing was performed on the child and no results for residual GAA activity are provided. Both parents are heterozygous for a variant in GAA; one for p.Gly655del and one for p.Asp489Asn. It is unclear whether this family is also reported in PMID 22791670. [PubMed:22711147](#)

Curation History

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