

Variant: NM_000152.5(GAA):c.1211A>G (p.Asp404Gly)

Version: 1.0

CA401365192 [↗](#)

959950 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: eb575230-a9e5-477c-a8c9-b2b3b0f87e34

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HGVS expressions

NM_000152.5:c.1211A>G

NM_000152.5(GAA):c.1211A>G (p.Asp404Gly)

NC_000017.11:g.80108713A>G

CM000679.2:g.80108713A>G

NC_000017.10:g.78082512A>G

CM000679.1:g.78082512A>G

NC_000017.9:g.75697107A>G

NG_009822.1:g.12158A>G

ENST00000570803.6:c.1211A>G

ENST00000572080.2:c.1211A>G

ENST00000577106.6:c.1211A>G

ENST00000302262.8:c.1211A>G

ENST00000302262.7:c.1211A>G

ENST00000390015.7:c.1211A>G

NM_000152.3:c.1211A>G

NM_001079803.1:c.1211A>G

NM_001079804.1:c.1211A>G

NM_000152.4:c.1211A>G

NM_001079803.2:c.1211A>G

NM_001079804.2:c.1211A>G

NM_001079803.3:c.1211A>G

NM_001079804.3:c.1211A>G

Likely Pathogenic

Met criteria codes 6

PM2_Supporting

PP4_Moderate

PS3_Supporting

PP3

PM1

PM3

Not Met criteria codes 1

PM5

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**

Lysosomal Diseases VCEP

The NM_000152.5:c.1211A>G variant in GAA is a missense variant predicted to cause substitution of aspartic acid by glycine at amino acid 404 (p.Asp404Gly). It has been reported in two individuals from the same family with Pompe disease: an adult with documentation of deficient GAA and clinical features consistent with LOPD, and a child with documentation of deficient GAA and clinical features of IOPD; both individuals treated enzyme replacement therapy (PMID: 24384324) (PP4_moderate). Both individuals are compound heterozygous for the variant, the adult individual had the variant in trans with c.695+5G>T (phase confirmed) and the child had the variant in trans (phase confirmed) with a variant that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.1798C>T (PM3). The highest population minor allele frequency in gnomAD v4.1.0 is 0.000001695 (2/1179940 alleles) in the European (non-Finnish)] population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). This variant alters amino acid Asp404, a residue that crystallography studies have shown to be important in the active site of GAA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (<https://www.biorxiv.org/content/10.1101/212837v1.full.pdf>, PMID: 29061980) (PM1). When expressed in HEK293T cells, this variant resulted in normal intracellular amounts of 110 kDa precursor, 95 kDa intermediate, and 76 kDa mature forms of GAA but 12.6% wild type GAA activity in cells and 4.6% in culture media. This suggests that this variant results in a catalytic deficiency but does not impact GAA synthesis and processing. The computational predictor REVEL gives a score of 0.968 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: 959950 , 2-star review status) with 2 submitters classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert panel (specifications Version 2.0): PP4_moderate, PM3, PM2_supporting, PM1, PS3_supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 15, 2025)

Met criteria codes

PM2_Supporting		The highest population minor allele frequency in gnomAD v4.1.0 is 0.000001695 (2/1179940 alleles) in the European (non-Finnish)] population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP4_Moderate	 	At least 2 individuals with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in dry blood spot and muscle biopsy pathology consistent with Pompe disease (PMID: 24384324). One individual is an adult with diagnosis of late-onset Pompe disease receiving treatment with enzyme replacement therapy (ERT) and the other is a child diagnosed with CRIM-positive infantile-onset Pompe disease receiving treatment with ERT.
PS3_Supporting	 	Expression of the GAA cDNA variant in HEK293T cells resulted in 12.6% wild type GAA activity in cells and 4.6% in culture media; however, intracellular amounts of the 110kDa precursor, 95 kDa intermediate, and 76 kDa mature forms of GAA in variant transfected cells were similar to the wild type transfected cells, suggesting that this variant does not interfere with the synthesis and processing of GAA, but results in a catalytic deficiency. In patient samples, expression of GAA mRNA extracted from muscle was approximately 4-fold lower than age and gender matched controls by qRT-PCR.
PP3	 	The computational predictor REVEL gives a score of 0.968 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM1	 	This variant alters amino acid Asp404, a residue that crystallography studies have shown to be important in the active site of GAA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (https://www.biorxiv.org/content/10.1101/212837v1.full.pdf , PMID: 29061980) (PM1).

PM3	 	At least one individual with Pompe disease was compound heterozygous for the variant and another pathogenic variant confirmed in trans by parental testing. This variant has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP (ClinVar ID: 640911)
Not Met criteria codes		
PM5	 	Another missense variant [c.1210G>A, p.Asp404Asn] [PMIDs, ClinVar Variation ID: 657348 in the same codon has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP. PM5 not applied given that this is a known active site and PM1 is applied. Three different missense variants, c.1211A>C (p.Asp404Ala), c.1211A>T (p.Asp404Val), and c.1212C>G (p.Asp404Glu), in the same codon have been reported in patients with Pompe disease (see http://www.pompevariantdatabase.nl/).

Curation History 		
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