

Variant: *NM_000152.5(GAA):c.1210G>A (p.Asp404Asn)*

Version: 1.0

CA8815234 [↗](#)

657348 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 13d44d46-c6e9-4a49-af4b-41db6c72811b

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HGVS expressions

NM_000152.5(GAA):c.1210G>A (p.Asp404Asn)

NM_000152.5:c.1210G>A

NC_000017.11:g.80108712G>A

CM000679.2:g.80108712G>A

NC_000017.10:g.78082511G>A

CM000679.1:g.78082511G>A

NC_000017.9:g.75697106G>A

NG_009822.1:g.12157G>A

ENST00000570803.6:c.1210G>A

ENST00000572080.2:c.1210G>A

ENST00000577106.6:c.1210G>A

ENST00000302262.8:c.1210G>A

ENST00000302262.7:c.1210G>A

ENST00000390015.7:c.1210G>A

NM_000152.3:c.1210G>A

NM_001079803.1:c.1210G>A

NM_001079804.1:c.1210G>A

NM_000152.4:c.1210G>A

NM_001079803.2:c.1210G>A

NM_001079804.2:c.1210G>A

NM_001079803.3:c.1210G>A

NM_001079804.3:c.1210G>A

Pathogenic

Met criteria codes 6

PM2_Supporting PS3_Supporting

PP3 PP4_Moderate PM1

PM3_Strong

Not Met criteria codes 1

PM5

Evidence Links 1

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information !

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

Lysosomal Diseases VCEP

The NM_000152.5:c.1210G>A variant in GAA is a missense variant predicted to cause substitution of aspartate by asparagine at amino acid 404 (p.Asp404Asn). At least 9 individuals with Pompe disease have been reported with this variant including individuals with documentation of deficient GAA activity and/or combination of clinical features of IOPD and on enzyme replacement therapy (PMID: 16433701, 22538254, 25687635, 26497565, 29205646) (PP4_Moderate). Four patients with Pompe disease are compound heterozygous for the variant, phase unknown, and a variant in GAA that has been classified as pathogenic by the ClinGen LSD VCEP, including c.1064T>C (p.Leu355Pro) (PMIDs 22658377, 23787031, 31193175), c.2481+102_2646+31del (PMID 22538254, 31086307), c.2227C>T (p.Gln743Ter) (PMID 25687635, 29205646), and c.2560C>T (p.Arg854Ter) (PMID 26497565) (0.5 points). In addition, the variant was found in a child in trans with c.2432delT, and his father in trans with c.-32-13T>G (PMID 16433701) (PM3_Strong). The variant has also been reported in compound heterozygosity with c.1445C>T (p.Pro482Leu)(PMID 31086307), c.1979G>A (p.Arg660His) (PMID 31086307), and c.1924G>T (p.Val642Phe) (PMID 29122469). The allelic data from these patients will be used in the assessment of the second variant and is not included here to avoid circular logic. The highest population minor allele frequency in a continental population in gnomAD v2.1.1 is 0.00006 (1/15828 alleles) in the African population, which is lower than the ClinGen LSD 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 LSD VCEP (<https://www.biorxiv.org/content/10.1101/212837v1.full.pdf>, PMID: 29061980) (PM1). When expressed in COS or HEK293 cells, this variant resulted in normal intracellular amounts of 110 kDa precursor, 95 kDa intermediate and 76 kDa mature forms of GAA but <2% wild type activity of GAA indicating that this variant may impact protein function (PMID 19862843, 24384324)(PS3_Supporting). The computational predictor REVEL gives a score of 0.869 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Four different missense variants, c.1211A>G (p.Asp404Gly), 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/>). The data from this variant (c.1210G>A (p.Asp404Asn) will be used to support the classification of the other missense substitutions of Asp404 and is not included here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 657348, 2 star review status) with five 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 based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Storage Disorder Variant Curation Expert Panel (Specifications Version 2.0): PM3_Strong, PM1, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen LSD VCEP on Sept 21, 2022).

Met criteria codes

PM2_Supporting	✓	The highest population minor allele frequency in a continental population in gnomAD v2.1.1 is 0.00006 (1/15828 alleles) in the African population, which is lower than the ClinGen LSD VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PS3_Supporting	 ✓	<p>When expressed in COS or HEK293 cells, this variant resulted in normal intracellular amounts of 110 kDa precursor, 95 kDa intermediate and 76 kDa mature forms of GAA but <2% wild type activity of GAA indicating that this variant may impact protein function (PMID 19862843, 24384324)(PS3_Supporting).</p> <p>When expressed in HEK293 cells, the intracellular amounts of 110 kDa precursor, 95 kDa intermediate and 76 kDa mature forms of GAA were similar to that in normal cells but the GAA activity was not above that of negative controls (Fig. 3B) PubMed:24384324 </p>
PP3	 ✓	The computational predictor REVEL gives a score of 0.869 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate	 ✓	

At least 9 individuals with Pompe disease have been reported with this variant including individuals with documentation of deficient GAA activity and/or combination of clinical features of IOPD and on enzyme replacement therapy (PMID: 16433701, 22538254, 25687635, 26497565, 29205646) (PP4_Moderate)

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 LSD VCEP (https://www.biorxiv.org/content/10.1101/212837v1.full.pdf , PMID: 29061980) (PM1).
PM3_Strong			At least 4 patients with Pompe disease are compound heterozygous for the variant, phase unknown, and a variant in GAA that has been classified as pathogenic by the ClinGen LSD VCEP, including c.1064T>C (p.Leu355Pro) (PMIDs 22658377, 23787031, 31193175)(0.5 points), c.2481+102_2646+31del (PMID 22538254, 31086307) (0.5 points), c.2227C>T (p.Gln743Ter) (PMID 25687635, 29205646) (0.5 points), and c.2560C>T (p.Arg854Ter) (PMID 26497565) (0.5 points). In addition, the variant was found in a child in trans with c.2432delT, and his father in trans with c.-32-13T>G (PMID 16433701) (1 point). The variant has also been reported in compound heterozygosity with c.1445C>T (p.Pro482Leu)(PMID 31086307), c.1979G>A (p.Arg660His) (PMID 31086307), and c.1924G>T (p.Val642Phe) (PMID 29122469). The allelic data from these patients will be used in the assessment of the second variant and is not included here to avoid circular logic. Total 3 points for PM3 (PM3_Strong).

Not Met criteria codes

PM5			Four different missense variants, c.1211A>G (p.Asp404Gly), 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/). However, the data from this variant (c.1210G>A (p.Asp404Asn) will be used to support the classification of the other variants and is not included here to avoid circular logic.
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Curation History

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