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Variant: NM_000152.4(GAA):c.1856G>A (p.Ser619Asn)

Version: 1.0

CA8815500

370146 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 33866ffd-7544-4e71-b8bf-08ec379e04c8
Approved on: 2025/1/21
Published on: 2025/2/28

HGVS expressions

NM_000152.4:c.1856G>A
NM_000152.4(GAA):c.1856G>A (p.Ser619Asn)
NC_000017.11:g.80112679G>A
CM000679.2:g.80112679G>A
NC_000017.10:g.78086478G>A
CM000679.1:g.78086478G>A
NC_000017.9:g.75701073G>A
NG_009822.1:g.16124G>A
ENST00000570803.6:c.1856G>A
ENST00000572080.2:c.1856G>A
ENST00000577106.6:c.1856G>A
ENST00000302262.8:c.1856G>A
ENST00000302262.7:c.1856G>A
ENST00000390015.7:c.1856G>A
ENST00000570716.1:n.296G>A
ENST00000572080.1:c.244G>A
ENST00000572803.1:n.470G>A
NM_000152.3:c.1856G>A
NM_001079803.1:c.1856G>A
NM_001079804.1:c.1856G>A
NM_001079803.2:c.1856G>A
NM_001079804.2:c.1856G>A
NM_000152.5:c.1856G>A
NM_001079803.3:c.1856G>A
NM_001079804.3:c.1856G>A

Pathogenic

Met criteria codes 5

PS3_Moderate PP4_Moderate PM3_Strong PM2_Supporting 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.1856G>A variant in GAA is a missense variant predicted to cause substitution of serine by asparagine at amino acid 619 (p.Ser619Asn). At least five probands with symptoms consistent with late-onset-Pompe disease have been reported with this variant (PMIDs 24158270, 16838077, 25052852, 37087815,22194990), two with documented deficiency of GAA activity (PMIDs 24158270, 16838077) (PP4_Moderate). One of these probands is compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.-32-13T>G (PMID: 25052852). The other three patients are compound heterozygous with unknown phase for the variant and a variant classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.-32-13T>G, c.1655T>C (p.Leu552Pro) or c.1927G>A (p.Gly643Arg), respectively (PMIDs: 37087815, 16838077, 24158270) (PM3_Strong). The highest population minor allele frequency in gnomAD v4.0 is 0.0001875 (17/90678 alleles) in South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in COS7 cells resulted in <5% GAA activity in cells and <5% in medium, and evidence of abnormal synthesis and processing on Western blot, indicating that this variant may impact protein function (PMID 16838077 and 19862843)(PS3_Moderate). The computational predictor REVEL gives a score 0.744 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: 370146; 2-star review status) with 10 submitters classifying the variant as pathogenic, and 2 as likely pathogenic. In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): PM3_Strong, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on January 21, 2025)

Met criteria codes

PS3_Moderate	✔	Expression of the variant in COS cells resulted in <10% wild type GAA activity and evidence of abnormal GAA processing, indicating that this variant may impact protein function (PMIDs: 16838077 and 19862843) (PS3_Moderate).
PP4_Moderate	✔	At least 2 patient(s) with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, muscle samples (PMIDs: 24158270, 16838077) (PP4_Moderate).
PM3_Strong	✔	This variant has been detected in at least 4 individuals with Pompe disease. Of those individuals, 4 were compound heterozygous for the variant and a pathogenic variant and 1 of those were confirmed in trans by molecular analysis (2 points in total). (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.0 is 0.0001875 (17/90678 alleles) in South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score 0.744 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Curation History

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