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Variant: NM_000152.5(GAA):c.1933G>T (p.Asp645Tyr)

Version: 1.0

CA401369905

556386 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6a400462-a157-4b95-88e6-b314f08e2348
Approved on: 2024/12/19
Published on: 2025/2/28

HGVS expressions

NM_000152.5(GAA):c.1933G>T (p.Asp645Tyr)
NM_000152.5:c.1933G>T
NC_000017.11:g.80112920G>T
CM000679.2:g.80112920G>T
NC_000017.10:g.78086719G>T
CM000679.1:g.78086719G>T
NC_000017.9:g.75701314G>T
NG_009822.1:g.16365G>T
ENST00000570803.6:c.1933G>T
ENST00000572080.2:c.*71G>T
ENST00000577106.6:c.1933G>T
ENST00000302262.8:c.1933G>T
ENST00000302262.7:c.1933G>T
ENST00000390015.7:c.1933G>T
ENST00000570716.1:n.373G>T
ENST00000572080.1:c.352G>T
ENST00000572803.1:n.547G>T
NM_000152.3:c.1933G>T
NM_001079803.1:c.1933G>T
NM_001079804.1:c.1933G>T
NM_000152.4:c.1933G>T
NM_001079803.2:c.1933G>T
NM_001079804.2:c.1933G>T
NM_001079803.3:c.1933G>T
NM_001079804.3:c.1933G>T

Pathogenic

Met criteria codes 6

PS3_Moderate PP4_Moderate PM3_Strong PM2_Supporting PM5 PP3

Not Met criteria codes 1

PS1

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.1933G>T variant in GAA is a missense variant predicted to cause substitution of aspartic acid, by tyrosine at amino acid 645 (p.Asp645Tyr). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0000335 (2/59698 alleles) in the Admixed American population, which is lower than the ClinGen LD VCEP threshold for PM2_Supporting (<0.001) meeting this criterion (PM2_Supporting). This variant has been detected in at least 6 individuals with Pompe disease. Of those individuals, 4 were compound heterozygous for the variant and pathogenic variants (c.-32-13T>G and c.525delT) none of those were confirmed in trans. (PMID: 27711114, 17616415, 24715333). Two individuals were homozygous for the variant (PMID: 38250073) (PM3_Strong). At least three patients with this variant had documented GAA deficiency with <30% of normal mean control level of GAA activity in cultured fibroblasts or were noted to have deficient GAA activity but results were not provided (PMID: 17616415, 24715333). Another four patients were reported to be on enzyme replacement therapy for Pompe disease (PMID: 38250073, 29573408, 27711114, 24715333) (PP4_Moderate). Expression of the variant in COS cells resulted in 0% wild type GAA activity in cells and medium and evidence of abnormal GAA synthesis and processing), variant to be described as Class B (“potentially less severe), indicating that this variant may impact protein function (PMID: 18425781) (PS3_Moderate). The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Two different missense variants (c.1933G > A, p.Asp645Asn, ClinVar Variation ID 188728, PMID: 9535769, 15145338, 16860134, 17723315, 23601496, 25139343, 26497565) and (c.1933G>C, p.Asp645His, ClinVar Variation ID 189013, PMID: (PMID: 12897283, 7695647) in the same codon have been classified as pathogenic and likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 556386) 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, PP4_Moderate, PS3_Moderate, PM5, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 19, 2024)

Met criteria codes

PS3_Moderate	✔	Expression of the variant in COS cells resulted in 0% wild type GAA activity in cells and medium and evidence of abnormal GAA synthesis and processing), leading the variant to be described as Class B (“potentially less severe"), indicating that this variant may impact protein function (PMID: 18425781). (PS3_Moderate).
PP4_Moderate	✔	At least three patients with this variant had documented GAA deficiency with <30% of normal mean control level of GAA activity in cultured fibroblasts or were noted to have deficient GAA activity but results were not provided (PMID: 17616415, 24715333). Another four patients were reported to be on enzyme replacement therapy for Pompe disease (PMID: 38250073, 29573408, 27711114, 24715333). PP4_Moderate.
PM3_Strong	✔	This variant has been detected in at least 6 individuals with Pompe disease. Of those individuals, 4 were compound heterozygous for the variant and pathogenic variants (c.-32-13T>G and c.525delT) none of those were confirmed in trans. (1 point, PMID: 27711114, 17616415, 24715333). Two individuals were homozygous for the variant (1 point, PMID: 38250073) (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0000335 (2/59698 alleles) in the Admixed American population, which is lower than the ClinGen LD VCEP threshold for PM2_Supporting (<0.001) meeting this criterion (PM2_Supporting).
PM5	✔	

Two different missense variants (c.1933G > A, p.Asp645Asn, ClinVar Variation ID 188728, PMID: 9535769, 15145338, 16860134, 17723315, 23601496, 25139343, 26497565) and (c.1933G>C, p.Asp645His, ClinVar Variation ID 189013, PMID: (PMID: 12897283, 7695647) in the same codon has been classified as pathogenic and likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5).

PP3	ℹ	✔	The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification ℹ	Condition	Published Date	Version ℹ	Criteria Specification	Gene
View	NM_000152.5(GAA):c.1933G>T (p.Asp...	Pathogenic	Glycogen Storage Disease II	2025-02-28	1.0	ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2	GAA

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