The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000152.5(GAA):c.1537G>A (p.Asp513Asn)

Version: 1.0

CA8815361

960182 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: cb23e159-0b15-4dd6-9a2b-76eb5a5452e9
Approved on: 2023/7/18
Published on: 2023/7/18

HGVS expressions

NM_000152.5:c.1537G>A
NM_000152.5(GAA):c.1537G>A (p.Asp513Asn)
NC_000017.11:g.80110826G>A
CM000679.2:g.80110826G>A
NC_000017.10:g.78084625G>A
CM000679.1:g.78084625G>A
NC_000017.9:g.75699220G>A
NG_009822.1:g.14271G>A
ENST00000570803.6:c.1537G>A
ENST00000572080.2:c.1537G>A
ENST00000577106.6:c.1537G>A
ENST00000302262.8:c.1537G>A
ENST00000302262.7:c.1537G>A
ENST00000390015.7:c.1537G>A
NM_000152.3:c.1537G>A
NM_001079803.1:c.1537G>A
NM_001079804.1:c.1537G>A
NM_000152.4:c.1537G>A
NM_001079803.2:c.1537G>A
NM_001079804.2:c.1537G>A
NM_001079803.3:c.1537G>A
NM_001079804.3:c.1537G>A

Likely Pathogenic

Met criteria codes 5

PP4_Moderate | PM5_Supporting | PP3 | PM3_Strong | PM2_Supporting

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.1537G>A variant in GAA is a missense variant predicted to cause substitution of aspartic acid by asparagine at amino acid 513 (p.Asp513Asn). This variant has been detected in at least five individuals with Pompe disease. One patient of late-onset Pompe disease had documented GAA deficiency as 8.7% of the normal control level of GAA activity (PMID 33301762). Three siblings from one family had documented reduced GAA enzyme activity within the deficient range (clinical laboratory data). Patient(s) with this variant had documented in a Pompe Registry with the onset of symptoms less than 12 years of age (PMID 31342611). (PP4_Moderate). Of those individuals, one individual was homozygous for the variant, and three siblings were compound heterozygous for the variant and the pathogenic c.-32-13T>G variant (PM3 2.0 points, PMID 33301762, clinical laboratory data) (PM3_Strong). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006533 (2/30616 alleles) in the South Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.861 which is above the threshold of 0.7, evidence that correlates with impact on GAA function (PP3). Another missense variant c.1538A>G (p.Asp513Gly) (PMID 31510962, 33560568; ClinVar Variation ID: 638014) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen LSD VCEP (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 960182). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP (specifications version 2.0): PP4_Moderate, PM3_Strong, PM2_Supporting, PP3, PM5_Supporting. (Classification approved by the ClinGen Lysosomal Diseases VCEP on July 18, 2023).

Met criteria codes

PP4_Moderate	✔	This variant has been detected in at least five individuals with Pompe disease. One patient of late-onset Pompe disease had documented GAA deficiency as 8.7% of the normal control level of GAA activity (PMID 33301762). Three siblings from one family had documented reduced GAA enzyme activity within the deficient range (Duke University Molecular Diagnostics Laboratory). Patient(s) with this variant had documented in a Pompe Registry with the onset of symptoms less than 12 years of age (PMID 31342611). (PP4_Moderate).
PM5_Supporting	✔	Another missense variant c.1538A>G (p.Asp513Gly) (PMID 31510962, 33560568; ClinVar Variation ID: 638014) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen LSD VCEP (PM5_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.861 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3_Strong	✔	This variant has been detected as homozygous in one individual with late-onset Pompe disease, and as compound heterozygous with the pathogenic c.-32-13T>G variant in three siblings with deficient GAA enzyme activity (PM3 2.0 points, PMID 33301762, Duke University Molecular Diagnostics Laboratory) (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006533 (2/30616 alleles) in the South Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Curation History

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