

Variant: *NM_000152.5(GAA):c.1538A>G (p.Asp513Gly)*

Version: 1.0

CA401367134 [↗](#)

638014 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e975a7b1-f5de-465e-b634-d374dae370a4

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HGVS expressions

NM_000152.5:c.1538A>G

NM_000152.5(GAA):c.1538A>G (p.Asp513Gly)

NC_000017.11:g.80110827A>G

CM000679.2:g.80110827A>G

NC_000017.10:g.78084626A>G

CM000679.1:g.78084626A>G

NC_000017.9:g.75699221A>G

NG_009822.1:g.14272A>G

ENST00000570803.6:c.1538A>G

ENST00000572080.2:c.1538A>G

ENST00000577106.6:c.1538A>G

ENST00000302262.8:c.1538A>G

ENST00000302262.7:c.1538A>G

ENST00000390015.7:c.1538A>G

NM_000152.3:c.1538A>G

NM_001079803.1:c.1538A>G

NM_001079804.1:c.1538A>G

NM_000152.4:c.1538A>G

NM_001079803.2:c.1538A>G

NM_001079804.2:c.1538A>G

NM_001079803.3:c.1538A>G

NM_001079804.3:c.1538A>G

Likely Pathogenic

Met criteria codes **5**

PP3

PM3

PM2_Supporting

PP4_Moderate

PS3_Supporting

Evidence Links **0**

Expert Panel

[Lysosomal Diseases VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1538A>G variant in GAA is a missense variant predicted to cause substitution of aspartic acid by glycine at amino acid 513 (p.Asp513Gly). This variant has been detected in two individuals with clinical features of Pompe disease. One patient with infantile-onset Pompe disease had documented GAA deficiency with 0%, less than 10% of normal mean control level of GAA activity in leukocytes (PMID 31510962). The other patient had documented deficient GAA enzyme activity, muscle weakness, and cardiomyopathy at 11 months old (clinical laboratory data). (PP4_Moderate). These two individuals were homozygous for the variant (PM3 1.0 point, PMID 31510962, clinical laboratory data) (PM3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). Expression of the variant in COS-7 cells resulted in 0.76% wild type GAA activity in cells and 0% in medium (<5%), and evidence of abnormal GAA synthesis and processing on Western blot, leading the variant to be described as Class B “potentially less severe” (Table 4), indicating that this variant may impact protein function (PMID 31510962) (PS3_Supporting). The computational predictor REVEL gives a score of 0.965 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: 638014). 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, PM2_Supporting, PS3_Supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases VCEP on July 18, 2023)

Met criteria codes

PP3			The computational predictor REVEL gives a score of [0.965] which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3			This variant has been detected as homozygous in one individual with infantile-onset Pompe disease and in one individual with deficient GAA enzyme activity and clinical features of Pompe disease (PM3 1.0 points, PMID 31510962, clinical laboratory data) (PM3).
PM2_Supporting			This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PP4_Moderate			One patient with infantile-onset Pompe disease had documented GAA deficiency with 0%, less than 10% of normal mean control level of GAA activity in leukocytes (PMID 31510962). The other patient had documented deficient GAA enzyme activity, muscle weakness, and cardiomyopathy at 11 months old (clinical laboratory data). (PP4_Moderate)
PS3_Supporting			Expression of the variant in COS-7 cells resulted in 0.76% wild type GAA activity in cells and 0% in medium (<5%), and evidence of abnormal GAA synthesis and processing on Western blot, leading the variant to be described as Class B “potentially less severe” (Table 4), indicating that this variant may impact protein function (PMID 31510962) (PS3_Supporting).

Curation History

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