

Variant: NM_000152.5(GAA):c.1465G>A (p.Asp489Asn)

Version: 1.0

CA220390 [↗](#)

92465 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 8f5d297d-fcfe-4bf7-ba17-fde165ab1525

Approved on: 2023/2/7

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HGVS expressions

NM_000152.5:c.1465G>A

NM_000152.5(GAA):c.1465G>A (p.Asp489Asn)

NC_000017.11:g.80110754G>A

CM000679.2:g.80110754G>A

NC_000017.10:g.78084553G>A

CM000679.1:g.78084553G>A

NC_000017.9:g.75699148G>A

NG_009822.1:g.14199G>A

ENST00000570803.6:c.1465G>A

ENST00000572080.2:c.1465G>A

ENST00000577106.6:c.1465G>A

ENST00000302262.8:c.1465G>A

ENST00000302262.7:c.1465G>A

ENST00000390015.7:c.1465G>A

NM_000152.3:c.1465G>A

NM_001079803.1:c.1465G>A

NM_001079804.1:c.1465G>A

NM_000152.4:c.1465G>A

NM_001079803.2:c.1465G>A

NM_001079804.2:c.1465G>A

NM_001079803.3:c.1465G>A

NM_001079804.3:c.1465G>A

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP4_Moderate

PM3_Very Strong

PS3_Moderate

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**

Lysosomal Diseases VCEP

The NM_000152.5:c.1465G>A variant in GAA is a missense variant that is predicted to result in the substitution of aspartate by asparagine at amino acid 489 (p.Asp489Asn). This variant has been detected in at least 10 patients reported to have Pompe disease including 7 individuals with reported laboratory values demonstrating deficient GAA activity (PMID: 17151339, 22081099, 22658377, 24395639, 24844452, 24923245, 29422078, 31193175), and three for whom GAA activity was not reported but who were treated by enzyme replacement (PMIDs: 25626711, 28574618). Nine individuals were compound heterozygous, phase unknown, for the variant and a variant that has been classified as pathogenic by the ClinGen LSD VCEP including c.-32-13T>G (PMIDs: 16917947, 2208109, 24395639, 24844452, 24923245, 28574618), c.40_47del8 (PMID: 29422078), c.307T>G (p.Cys103Gly) (PMID: 18429042), c.1799G>A (p.Arg600His) (PMID: 22711147), c.2014C>T (p.Arg672Trp) (PMID: 16917947, 2208109), and another individual was compound heterozygous for the variant and c.2481+110_2646+39del (labeled as c.IVS17 + 102_IVS18 + 31 in the paper) confirmed in trans (PMID: 25626711). The variant was also detected in a parent of two affected children, now deceased, with c.1962_1964delAGA (p.Glu655del) in the other parent. However, as these variants were not confirmed to be present in the affected children, the data is not included (PMID: 22711147). Another individual was reported to have the variant but the cDNA sequence was not provided (PMID: 17616415 (PM3_VeryStrong)). The highest population minor allele frequency in gnomAD is 0.00005 (1/21638) in the European Finnish population which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). In two different studies, this variant results in <2% GAA activity when expressed in COS-7 cells or Ad5-SV40 immortalized human GAA-deficient fibroblasts and, on Western blot, most of the gene product remained as the 110 kDa inactive precursor (PMID: 17915575, 19862843) (PS3_Moderate). The computational predictor REVEL gives a score of 0.938 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: 92465). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP (specifications version 2.0): PM3_VeryStrong, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen LSD VCEP, February 7, 2023).

Met criteria codes

PM2_Supporting		The highest population minor allele frequency in gnomAD is 0.00005 (1/21638) in the European Finnish population which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4_Moderate		This variant has been detected in at least 10 patients reported to have Pompe disease including 7 individuals with reported laboratory values demonstrating deficient GAA activity (PMID: 17151339, 22081099, 22658377, 24395639, 24844452, 24923245, 29422078, 31193175), and three for whom GAA activity was not reported but who were treated by enzyme replacement (PMIDs: 25626711, 28574618).
PM3_Very Strong		Nine individuals were compound heterozygous, phase unknown, for the variant and a variant that has been classified as pathogenic by the ClinGen LSD VCEP including c.-32-13T>G (PMIDs: 16917947, 2208109, 24395639, 24844452, 24923245, 28574618) (max 2 x 0.5 points), c.40_47del8 (PMID: 29422078) (0.5), c.307T>G (p.Cys103Gly) (PMID: 18429042) (0.5 points), c.1799G>A (p.Arg600His) (PMID: 22711147) (0.5 points), c.2014C>T (p.Arg672Trp) (PMID: 16917947, 2208109) (0.5 points), and another individual was compound heterozygous for the variant and c.2481+110_2646+39del (labeled as c.IVS17 + 102_IVS18 + 31 in the paper) confirmed in trans (PMID: 25626711) (1 point). The variant was also detected in a parent of two affected children, now deceased, with c.1962_1964delAGA (p.Glu655del) in the other parent. However, as these variants were not confirmed to be present in the affected children, the data is not included (PMID: 22711147). Another individual was reported to have the variant but the cDNA sequence was not provided (PMID: 17616415). Total points: 4.5 (PM3_VeryStrong).
PS3_Moderate		In two different studies, this variant results in <2% GAA activity when expressed in COS-7 cells or an Ad5-SV40 immortalized human GAA-deficient fibroblast and, on Western blot, most of the gene product remained as the 110

kDa inactive precursor (PMID: 17915575, 19862843) (PS3_Moderate).

PP3



The computational predictor REVEL gives a score of 0.938 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Curation History [↗](#)

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Showing 1 to 1 of 1 rows

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