

Variant: *NM_000152.5(GAA):c.-32-13T>G*

Version: 1.0

CA116606 [↗](#)

4027 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: a7e79754-98a1-4349-ad1a-8750336207bf

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HGVS expressions

NM_000152.5(GAA):c.-32-13T>G

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NC_000017.11:g.80104542T>G

CM000679.2:g.80104542T>G

NC_000017.10:g.78078341T>G

CM000679.1:g.78078341T>G

NC_000017.9:g.75692936T>G

NG_009822.1:g.7987T>G

ENST00000570803.6:c.-32-13T>G

ENST00000572080.2:c.-32-13T>G

ENST00000577106.6:c.-32-13T>G

ENST00000302262.8:c.-32-13T>G

ENST00000302262.7:c.-32-13T>G

ENST00000390015.7:c.-32-13T>G

ENST00000570803.5:c.-32-13T>G

ENST00000577106.5:c.-32-13T>G

NM_000152.3:c.-32-13T>G

NM_001079803.1:c.-32-13T>G

NM_001079804.1:c.-32-13T>G

NM_000152.4:c.-32-13T>G

NM_001079803.2:c.-32-13T>G

NM_001079804.2:c.-32-13T>G

NM_001079803.3:c.-32-13T>G

NM_001079804.3:c.-32-13T>G

Pathogenic

Met criteria codes **3**

PM3_Very Strong

PP4_Moderate

PVS1_Strong

Not Met criteria codes **2**

PS1

BS1

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**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.-32-13T>G variant occurs in the acceptor splice site region of intron 1 of GAA and results in a reduced level of normally spliced GAA transcripts (“leaky splicing”) allowing for the production of residual GAA activity. This variant, historically termed IVS1-13T>G and -45T>G, is the most common GAA variant identified in patients with late-onset Pompe disease; about 36-90% of individuals with late-onset Pompe disease are heterozygous for this variant (PMID: 20301438, 31342611). Haplotype analysis suggests that c.-32-13T>G has arisen at least twice (PMID: 17210890). RT-PCR analysis of fibroblast RNA from patients with the variant, in addition to minigene studies assessing the splicing impact of c.-32-13T>G, have identified various aberrantly spliced transcripts as well as a low level of the normal transcript. The aberrant splice variants include SV1, which retains the first 36 nt of intron 1 and lacks exon 2; SV2, in which exon 2 is completely spliced out; and SV3, in which exon 2 is partially spliced out. The same aberrant splicing variants, missing all or part of exon 2, have also been found at low levels in the RNA of unaffected individuals and when the normal GAA sequence is analyzed in minigene studies (PMID: 7717400, 8817337, 17210890, 24150945). Overall, the variant appears to reduce the level of normal GAA transcripts to about 10-20% of wild type. This “leaky splicing” allows for some active GAA enzyme to be produced, thereby delaying onset of symptoms in individuals who carry this variant. It should be noted that these in vitro observations pertain to data collected in non muscle cell lines, the precise effect that this variant may have in vivo within muscle is not known. In cells from patients and cells transfected with the variant, antisense oligonucleotides and other treatments have been shown to increase the level of exon 2 inclusion, producing correctly spliced transcripts; to increase the residual activity of GAA; and to reduce the level of glycogen (PMID: 24150945, 28624228, 28629821, 31301153, 32317649, 33426149, 36401034). Based on the accumulation of evidence, PVS1 is applied at strong (PMID: 37352859). Hundreds of patients with this variant have been reported in the literature (see list of publications in <https://www.pompevariantdatabase.nl/>). There are numerous of examples of affected patients who are heterozygous for c.-32-13T>G and another variant in GAA that has been classified as pathogenic by the ClinGen LD GCEP (pathogenic classification does not require use of c.-32-13T>G for PM3). To provide some examples, the variant has been found in compound heterozygosity with c.525delT (ClinVar Variation ID: 4033, SCV001443331.1) (4 probands; max 2 x 0.5 points) (PMID: 27189384), c.1051delG (ClinVar Variation ID: 188841, SCV001371764.1) (0.5 points) (PMID: 27189384), c.2481+102_2646+31del (ClinVar Variation ID: 657307) (0.5 points) (PMID: 27189384), c.2331+2T>A (ClinGen Variation ID: 371281) (2 probands) (2 x 0.5 points) (PMID: 27189384), c.1548G>A (p.Trp516Ter) (ClinVar Variation ID: 189025, SCV001371740.1) (0.5 points) (PMID: 27189384), c.1441T>C (p.Trp481Arg) (ClinVar Variation ID: 189007, SCV004227917.1) (0.5 points) (PMID: 27189384), c.1551+1G>C (ClinVar Variation ID: 554983) (0.5 points) (PMID: 7881425), c.784G>A (p.Glu262Lys) (ClinVar Variation ID: 188806, SCV002032128.1) (0.5 points) (PMID: 25673129), and c.670C>T (p.Arg224Trp) (Variation ID: 189188, SCV001371775.1) (0.5 points) (PMID: 25673129), as well as homozygous individuals (max 2 x 0.5 points) (PMID: 25673129, 26231297 34405923). >7 points (PM3_VeryStrong). While the variant has never been associated with classical infantile-onset Pompe disease, the age of onset and severity of disease in patients with the variant can vary widely, even in individuals who are compound heterozygous for c.-32-13T>G and a complete loss of function variant (PMID: 17210890, 34405923). Clinically affected patients who are homozygous for the variant have also been reported. However, some homozygous individuals appear to remain asymptomatic, leading to discussions on how best to follow these individuals if identified on newborn screen (PMID: 30922962). Studies indicate that one of the factors that can modify the phenotype is the presence of another variant, c.510C>T, in cis with c.-32-13T>G. This variant has been shown to further reduce the level of normal GAA mRNA causing early onset and greater severity of symptoms (PMID: 30922962). The highest minor allele frequency (MAF) in gnomAD v2.1.1. is 0.005293 (614/116004 alleles) in the European non-Finnish population, with one homozygote in the “remaining individuals” group. In gnomAD v4.1.0, the highest population MAF is 0.006355 (7335/1154180 alleles; 19 homozygotes) in the European non-Finnish population. Although this allele frequency meets the BS1 threshold suggested by the LD VCEP, the fact that this variant is the most common variant in individuals with late onset Pompe disease accounts for the population based allele frequency that is observed. Therefore, BS1 was not applied. In addition there is abundant evidence to support its pathogenicity. Other variants in the same splice region have been identified in patients with Pompe disease including c.-32-3C>G, c.-32-3C>A, c.-32-2A>G, and c.-32-1G>C (PMID: 31301153, 33560568). The classification of c.-32-13T>G will be used to support the classification of these other variants. Therefore, to avoid circular logic, their classification was not used in the classification of c.-32-13T>G. There is a ClinVar entry for this variant (Variation ID: 4027). In summary, the c.-32-13T>G variant (also known as IVS1-13T>G) meets the criteria to be classified as pathogenic for Pompe disease. It results in residual GAA activity and is the most common GAA variant causing late-onset Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications version 2.0): PVS1_Strong,

Met criteria codes

PM3_Very Strong			There are numerous of examples of affected patients who are heterozygous for c.-32-13T>G and another variant in GAA that has been classified as pathogenic by the ClinGen LD GCEP (pathogenic classification does not require use of c.-32-13T>G for PM3). To provide some examples, the variant has been found in compound heterozygosity with c.525delT (ClinVar Variation ID: 4033, SCV001443331.1) (4 probands; max 2 x 0.5 points) (PMID: 27189384), c.1051delG (ClinVar Variation ID: 188841, SCV001371764.1) (0.5 points) (PMID: 27189384), c.2481+102_2646+31del (ClinVar Variation ID: 657307) (0.5 points) (PMID: 27189384), c.2331+2T>A (ClinGen Variation ID: 371281) (2 probands) (2 x 0.5 points) (PMID: 27189384), c.1548G>A (p.Trp516Ter) (ClinVar Variation ID: 189025, SCV001371740.1) (0.5 points) (PMID: 27189384), c.1441T>C (p.Trp481Arg) (ClinVar Variation ID: 189007, SCV004227917.1) (0.5 points) (PMID: 27189384), c.1551+1G>C (ClinVar Variation ID: 554983) (0.5 points) (PMID: 7881425), c.784G>A (p.Glu262Lys) (ClinVar Variation ID: 188806, SCV002032128.1) (0.5 points) (PMID: 25673129), and c.670C>T (p.Arg224Trp) (Variation ID: 189188, SCV001371775.1) (0.5 points) (PMID: 25673129), as well as homozygous individuals (max 2 x 0.5 points)(PMID: 25673129, 26231297 34405923). >7 points (PM3_VeryStrong). X points (PM3_Very Strong). Data from hundreds of additional patients is available in the literature but PM3 has already been applied at the highest strength.
PP4_Moderate			This variant, historically termed IVS1-13T>G, is the most common GAA variant identified in patients with late-onset Pompe disease; about 36-90% of individuals with late-onset Pompe disease are heterozygous for this variant (Reuser et al, 2019, PMID: 31342611; Leslie and Bailey, 2023, PMID: 20301438). Hundreds of patients with this variant have been reported in the literature (see list of publications in https://www.pompevariantdatabase.nl/). It has routinely been described in individuals with symptoms consistent with late onset Pompe disease with documented laboratory values of GAA activity in the affected range. While the variant has never been associated with classical infantile-onset Pompe disease, the age of onset and severity of disease in patients with the variant can vary widely (PMID: 17210890, 34405923) (PP4_Moderate).
PVS1_Strong			The NM_000152.5:c.-32-13T>G variant occurs in the acceptor splice site region of intron 1 of GAA and results in a reduced level of normally spliced GAA transcripts (“leaky splicing”) allowing for the production of residual GAA activity. RT-PCR analysis of fibroblast RNA from patients with the variant, in addition to minigene studies assessing the splicing impact of c.-32-13T>G, have identified various aberrantly spliced transcripts as well as a low level of the normal transcript. The aberrant splice variants include SV1, which retains the first 36 nt of intron 1 and lacks exon 2; SV2, in which exon 2 is completely spliced out; and SV3, in which exon 2 is partially spliced out. The same aberrant splicing variants, missing all or part of exon 2, have also been found at low levels in the RNA of unaffected individuals and when the normal GAA sequence is analyzed in minigene studies (PMID: 7717400, 8817337, 17210890, 24150945). Overall, the variant appears to reduce the level of normal GAA transcripts to about 10-20% of wild type. This “leaky splicing” allows for some active GAA enzyme to be produced, thereby delaying onset of symptoms in individuals who carry this variant. It should be noted that these in vitro observations pertain to data collected in non muscle cell lines, the precise effect that this variant may have in vivo within muscle is not known. In cells from patients and cells transfected with the variant, antisense oligonucleotides and other treatments have been shown to increase the level of exon 2 inclusion, producing correctly spliced transcripts; to increase the residual activity of GAA; and to reduce the level of glycogen (PMID: 24150945, 28624228, 28629821, 31301153, 32317649, 33426149, 36401034). Based on the accumulation of evidence, PVS1 is applied at strong (PMID: 37352859).

Not Met criteria codes

PS1		
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Other variants in the same splice region have been identified in patients with Pompe disease including c.-32-3C>G, c.-32-3C>A, c.-32-2A>G, and c.-32-1G>C (PMID: 31301153, 33560568). The classification of c.-32-13T>G will be used to support the classification of these other variants. Therefore, to avoid circular logic, their classification was not used in the classification of c.-32-13T>G.

BS1



The highest minor allele frequency (MAF) in gnomAD v2.1.1. is 0.005293 (614/116004 alleles) in the European non-Finnish population, with one homozygote in the “remaining individuals” group. In gnomAD v4.1.0, the highest population MAF is 0.006355 (7335/1154180 alleles; 19 homozygotes) in the European non-Finnish population. Although this frequency meets the BS1 threshold for the LD VCEP, this variant, as by far the most common variant in individuals with late onset Pompe disease and abundant evidence to support its’ pathogenicity, is an exception. Therefore, BS1 was not applied.

Curation History [↗](#)

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