Variant: NM_000152.5(GAA):c.546+1G>T

Version: 1.0

CA401361913

3241650 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: fa6294cc-492f-4f73-aa81-7dcda9dd4721
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HGVS expressions

NM_000152.5:c.546+1G>T
NM_000152.5(GAA):c.546+1G>T
NC_000017.11:g.80105133G>T
CM000679.2:g.80105133G>T
NC_000017.10:g.78078932G>T
CM000679.1:g.78078932G>T
NC_000017.9:g.75693527G>T
NG_009822.1:g.8578G>T
ENST00000570803.6:c.546+1G>T
ENST00000572080.2:c.546+1G>T
ENST00000577106.6:c.546+1G>T
ENST00000302262.8:c.546+1G>T
ENST00000302262.7:c.546+1G>T
ENST00000390015.7:c.546+1G>T
ENST00000570803.5:c.546+1G>T
ENST00000577106.5:c.546+1G>T
NM_000152.3:c.546+1G>T
NM_001079803.1:c.546+1G>T
NM_001079804.1:c.546+1G>T
NM_000152.4:c.546+1G>T
NM_001079803.2:c.546+1G>T
NM_001079804.2:c.546+1G>T
NM_001079803.3:c.546+1G>T
NM_001079804.3:c.546+1G>T

Pathogenic

Met criteria codes 4

PVS1 PM3 PP4_Moderate 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.546+1G>T variant in GAA occurs within the canonical splice donor site of intron 2. Two studies involving minigene analysis have showed that the variant disrupts normal splicing, resulting in skipping of exon 2 (PMID: 31301153, 39905333). Exon 2 contains the start methionine and signal sequence for GAA (amino acids 1-27; https://www.uniprot.org/uniprot/P10253). Deletion of exon 2 causes complete loss of enzyme activity when expressed in heterologous cells (Huie et al, 1994, PMID 7881425; Boerkoel et al, 1995, PMID 7717400) (PVS1). At least 5 probands with symptoms consistent with late-onset Pompe disease have been reported with this variant (PMID: 18285536, 25396301, 25712382, 28838325), one with documented GAA deficiency with <10% of normal mean control level of GAA activity in a muscle sample (PP4_Moderate). Of those individuals, 4 were compound heterozygous for this variant and another variant in GAA, c.-32-13T>G (ClinVar Variation ID: 4027), which is classified as pathogenic by the ClinGen Lysosomal Diseases VCEP. The phase is unconfirmed in all cases (PMID: 18285536, 25396301, 25712382, 28838325) (PM3). Additionally, this variant is absent in gnomAD v4.1.0. (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 3241650). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0.0): PVS1, PM2_Supporting, PM3, PP4_Moderate. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on July 1, 2025)

Met criteria codes

PVS1	✔	The NM_000152.5:c.546+1G>T variant in GAA occurs within the canonical splice donor site of intron 2. Two studies involving minigene analysis have showed that the variant disrupts normal splicing, resulting in skipping of exon 2 (PMID: 31301153, 39905333). Exon 2 contains the start methionine and signal sequence for GAA (amino acids 1-27; https://www.uniprot.org/uniprot/P10253). Deletion of exon 2 causes complete loss of enzyme activity when expressed in heterologous cells (Huie et al, 1994, PMID 7881425; Boerkoel et al, 1995, PMID 7717400) (PVS1).
PM3	✔	This variant has been detected in at least 5 individuals with Pompe disease. Of those individuals, 4 were compound heterozygous for this variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.-32-13T>G, phase unconfirmed (PMID: 18285536, 25396301, 25712382, 28838325; max 2 x 0.5 points) (PM3).
PP4_Moderate	✔	At least 5 probands with symptoms consistent with late-onset Pompe disease have been reported with this variant (PMID: 18285536, 25396301, 25712382, 28838325), one with documented GAA deficiency with <10% of normal mean control level of GAA activity in a muscle sample (PP4_Moderate).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Curation History

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