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:c.2T>C

Version: 2.0

CA401359804

984802 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 29feb6c3-10a4-4799-9ca8-6c365f460b86
Approved on: 2023/4/4
Published on: 2023/4/5

HGVS expressions

NM_000152.5:c.2T>C
NC_000017.11:g.80104588T>C
CM000679.2:g.80104588T>C
NC_000017.10:g.78078387T>C
CM000679.1:g.78078387T>C
NC_000017.9:g.75692982T>C
NG_009822.1:g.8033T>C
ENST00000570803.6:c.2T>C
ENST00000572080.2:c.2T>C
ENST00000577106.6:c.2T>C
ENST00000302262.8:c.2T>C
ENST00000302262.7:c.2T>C
ENST00000390015.7:c.2T>C
ENST00000570803.5:c.2T>C
ENST00000577106.5:c.2T>C
NM_000152.3:c.2T>C
NM_001079803.1:c.2T>C
NM_001079804.1:c.2T>C
NM_000152.4:c.2T>C
NM_001079803.2:c.2T>C
NM_001079804.2:c.2T>C
NM_001079803.3:c.2T>C
NM_001079804.3:c.2T>C

Pathogenic

Met criteria codes 4

PM2_Supporting PP4 PVS1 PM3

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.2T>C variant in GAA is an initiator codon variant that is predicted to abolish the start codon (p.Met1?). The next in-frame methionine is at position 122 but, even if used, the gene product would be missing the signal sequence (PMID 22252923). This variant results in 3.6% GAA activity in medium and 0% GAA activity in cells and is abnormally synthesized when expressed in HEK293 cells, and is classified as Class B (“potentially less severe”) by Kroos et al, 2012 (PMID: 22644586) PVS1_Strong for initiator codon variant in GAA upgraded to PVS1 based on availability of functional evidence (PVS1). Two patients with the variant have been reported in the literature, both with late-onset Pompe disease. One had diminished GAA activity, but residual activity was not provided (PMID: 29124014). The second patient had documented laboratory values indicating reduced GAA activity but was also heterozygous for a pseudodeficiency variant. The patient was on enzyme replacement therapy (PMID: 21757382) (PP4). Two patients are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, including c.1826dup (p.Tyr609Ter) (PMID: 29124014) and c.1935C>A (p.Asp645Gln) (PMID: 21757382). The phase was not confirmed in either case (PM3). The variant is absent in gnomAD v2.1.1 (PM2_Supporting). Of note, additional initiator codon variants, including c.1A>G, c.1A>T, and c.3G>A, have been reported in patients with Pompe disease (see http://www.pompevariantdatabase.nl/). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP: PVS1, PM3, PP4, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Disease Variant Curation Expert Panel, April 4, 2023).

Met criteria codes

PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PP4	✔	Two patients with the variant have been reported in the literature, both with late-onset Pompe disease. One had diminished GAA activity, but residual activity was not provided (PMID: 29124014). The second patient had documented laboratory values indicating reduced GAA activity but was also heterozygous for a pseudodeficiency variant. The patient was on enzyme replacement therapy (PMID: 21757382) (PP4).
PVS1	✔	The NM_000152.5:c.2T>C variant in GAA is an initiator codon variant that is predicted to abolish the start codon (p.Met1?). The next in-frame methionine is at position 122 but, even if used, the gene product would be missing the signal sequence (PMID 22252923). This variant results in 3.6% GAA activity in medium and 0% GAA activity in cells and is abnormally synthesized when expressed in HEK293 cells, and is classified as Class B (“potentially less severe”) by Kroos et al, 2012 (PMID: 22644586). PVS1_Strong for initiator codon variant upgraded to PVS1 based on availability of functional evidence (PVS1).
PM3	✔	Two patients are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, including c.1826dup (p.Tyr609Ter) (PMID: 29124014) and c.1935C>A (p.Asp645Gln) (PMID: 21757382). The phase was not confirmed in either case. Totals 2 x 0.5 = 1 point (PM3).

Curation History

Showing 1 to 4 of 4 rows

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