Variant: NM_000152.5(GAA):c.2237G>C (p.Trp746Ser)

Version: 1.0

CA198797

188484 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: cf4180ea-cd17-4bc3-9c7c-5edb5dfa847c
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HGVS expressions

NM_000152.5:c.2237G>C
NM_000152.5(GAA):c.2237G>C (p.Trp746Ser)
NC_000017.11:g.80117015G>C
CM000679.2:g.80117015G>C
NC_000017.10:g.78090814G>C
CM000679.1:g.78090814G>C
NC_000017.9:g.75705409G>C
NG_009822.1:g.20460G>C
ENST00000570803.6:c.2237G>C
ENST00000572080.2:c.*375G>C
ENST00000577106.6:c.2237G>C
ENST00000302262.8:c.2237G>C
ENST00000302262.7:c.2237G>C
ENST00000390015.7:c.2237G>C
ENST00000572080.1:c.656G>C
ENST00000573556.1:n.190G>C
NM_000152.3:c.2237G>C
NM_001079803.1:c.2237G>C
NM_001079804.1:c.2237G>C
NM_000152.4:c.2237G>C
NM_001079803.2:c.2237G>C
NM_001079804.2:c.2237G>C
NM_001079803.3:c.2237G>C
NM_001079804.3:c.2237G>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PM3 PM5 PP4_Moderate PP3

Not Met criteria codes 1

PS3

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.2237G>C variant in GAA is a missense variant predicted to result in the substitution of tryptophan by serine at amino acid 746 (p.Trp746Ser). This variant has been reported in at least 11 patients with late onset Pompe disease (LOPD) (PMID: 18425781, 22081099, 24169249, 28490439, 33344388, 34020684), with two having GAA enzyme activity <10% in muscle (PMID: 22081099) (PP4_Moderate). One Chinese patient with LOPD was compound heterozygous for the variant and a nonsense pathogenic variant c.2237G>A (p.Trp746*) at the same nucleotide; however, this patient has a third variant c.503G>A (p.Arg168Gln) with no phase information (PMID: 24169249), so it's not used for PM3 point counting. Another Chinese patient was compound heterozygous for the variant (maternally inherited) and a pathogenic variant c.1935C>A (p.Asp645Glu) (paternally inherited) (PMID: 33344388); and it's not used for PM3 point counting due to the complex phenotype and the lack other evidence supporting the diagnosis of LOPD. A third Chinese individual heterozygous for the variant, a pathogenic variant c.2662G>T (p.Glu888*), and a third variant c.2647-7G>A was detected by genome sequencing as newborn screening; and it's not used for PM3 point counting due to the lack of phenotype information. Six Italian patients (PMID: 22081099) and one Spanish patient (PMID: 34020684) with LOPD were heterozygous for the variant and c.-32-13T>G pathogenic variant with no phase information (1 point, max for homozygous patients) (PM3). Expression of the variant in COS or HEK293 cells resulted in 2% residual GAA activity in medium and 0.1% normal activity in cells and evidence of abnormal GAA synthesis and processing, leading to a Class B ("potentially less severe") classification (PMID: 22644586). However, another in vitro study reported the variant as a "relatively mild mutation" but also class E "probably non-pathogenic" (PMID: 23430493). Functional criteria is not applied due to inconsistent functional classification. The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001733 (13/75034) in the African/African American population which is lower than the ClinGen Lysosomal Diseases Variant Curation Expert Panel (LD VCEP) threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.919 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). A different missense variant c.2238G>C (p.Trp746Cys) on the same amino acid has been classified as pathogenic by the LD VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 188484; 2 star review status) with 7 submitters classifying the variant as pathogenic and 5 as likely pathogenic. In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen LD VCEP (Specifications Version 2.0): PM3, PM5, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen LD VCEP - Dec. 17, 2024).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0001733 (13/75034) in the African/African American population which is lower than the ClinGen LD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PM3	✔	Six Italian patients (PMID: 22081099) and one Spanish patient (PMID: 34020684) with LOPD were heterozygous for the variant and c.-32-13T>G pathogenic variant with no phase information, and they are capped to 1 PM3 point to avoid over-counting if these two variants are in-cis. One Chinese patient with LOPD was compound heterozygous for the variant and a nonsense pathogenic variant c.2237G>A (p.Trp746*) at the same nucleotide; however, this patient has a third variant c.503G>A (p.Arg168Gln) with no phase information (PMID: 24169249), and it's not used for PM3 point counting. Another Chinese patient was compound heterozygous for the variant (maternally inherited) and a pathogenic variant c.1935C>A (p.Asp645Glu) (paternally inherited) (PMID: 33344388); and it's not used for PM3 point counting due to the complex phenotype reported and the lack evidence supporting the diagnosis of LOPD. A third Chinese individual heterozygous for the variant, a pathogenic variant c.2662G>T (p.Glu888*), and a third variant c.2647-7G>A was detected by genome sequencing as newborn screening; and it's not used for PM3 point counting due to the lack of phenotype information.

PM5		✔	c.2238G>C (p.Trp746Cys) is classified as Pathogenic based on the guidelines of the ClinGen LD VCEP. Other missense changes at this position include p.Trp746Arg, p.Trp746Gly, and p.Trp746Leu.
PP4_Moderate		✔	This variant has been present in at least 11 patients with LOPD: 1 northern European (PMID: 18425781), 6 Italian (PMID: 22081099), one Chinese (PMID: 24169249), one northern European (PMID: 28490439), one south Chinese (PMID: 33344388), and one Spain (PMID: 34020684), and two of them had GAA enzyme activity <10% in muscle (PMID: 22081099).
PP3		✔	The computational predictor REVEL gives a score of 0.919 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PS3		✖	Expression of the variant in COS or HEK293 cells resulted in <5% wild type GAA activity and evidence of abnormal GAA synthesis and processing, leading to a Class B ("potentially less severe") classification (PMID: 22644586). The Erasmus database confirms 0.1% normal activity in cells. However, contradictory results were published in PMID: 23430493; reporting the variant as a "relatively mild mutation" but also Class E, which is "probably non-pathogenic". Functional criteria was not applied due to discrepancy.

Curation History

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