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Variant: NM_000152.5(GAA):c.2297A>C (p.Tyr766Ser)

Version: 1.0

CA8815680

420102 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: ad356d09-5ea4-40e4-920a-d04aa5815cbf
Approved on: 2022/6/3
Published on: 2022/6/3

HGVS expressions

NM_000152.5(GAA):c.2297A>C (p.Tyr766Ser)
NM_000152.5:c.2297A>C
NC_000017.11:g.80117075A>C
CM000679.2:g.80117075A>C
NC_000017.10:g.78090874A>C
CM000679.1:g.78090874A>C
NC_000017.9:g.75705469A>C
NG_009822.1:g.20520A>C
ENST00000570803.6:c.2297A>C
ENST00000572080.2:c.*435A>C
ENST00000577106.6:c.2297A>C
ENST00000302262.8:c.2297A>C
ENST00000302262.7:c.2297A>C
ENST00000390015.7:c.2297A>C
ENST00000572080.1:c.716A>C
ENST00000573556.1:n.250A>C
NM_000152.3:c.2297A>C
NM_001079803.1:c.2297A>C
NM_001079804.1:c.2297A>C
NM_000152.4:c.2297A>C
NM_001079803.2:c.2297A>C
NM_001079804.2:c.2297A>C
NM_001079803.3:c.2297A>C
NM_001079804.3:c.2297A>C

Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4_Moderate PM3_Very Strong

Not Met criteria codes 1

PM5

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.2297A>C variant in GAA is a missense variant predicted to cause substitution of tyrosine by serine at amino acid 766 (p.Tyr766Ser). At least 12 patients with this variant have been reported including 7 with documented GAA deficiency with <1% of normal mean control level of GAA activity in cultured fibroblasts or GAA activity in the affected leukocytes or dried blood spot (PMID: 22538254, 22521436, 31875618, Clinical Laboratory data), one noted to have deficient GAA activity but results were not provided (PMID: 28394184), and two reported to have Pompe disease with no further details (PMID: 26693141). At least three of these patients are receiving enzyme replacement therapy (PMID: 22521436, 22538254, 26693141 29289479, 30214072, 31899940) (PP4_Moderate). Of the reported patients, at least three are homozygous (PMID: 22521436, 22538254, 26693141 29289479, 31899940, Clinical Laboratory data, and seven were compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LSD VCEP including c.1309C>T (p.Arg437Cys) (PMID: 22521436), c.-32-13T>G (Clinical Laboratory Data), c.2608C>T (p.Arg870Ter) (Clinical Laboratory Data), c.525delT (PMID: 30214072), all phase unknown, and c.1822C>T (p.Arg608Ter), confirmed in trans by parental testing (PMID: 31875618) (PM3_Very Strong). Two other individuals are compound heterozygous for the variant and either c.1118T>G (p.Leu373Arg) (Clinical Laboratory data) or c.2105G>A (p.Arg702His) (PMID: 28394184) but the allelic data from these patients will be used in the classification of the second variant and is not included here to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005441 (1/18378 alleles) in the East Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion. The computational predictor REVEL gives a score of 0.98 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). To our knowledge, the results of functional studies for this variant have not been published. Two other missense variants, c.2297A>G (p.Tyr766Cys) and 2296T>A (p.Tyr766Asn), in the same codon have been reported in patients with Pompe disease. The classification of c.2297A>C (p.Tyr766Ser) will be used to apply PM5 for those other variants and is not included here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 420102; 2 star review status) with five submitters classifying the variant as pathogenic and one as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Storage Disorders Expert Panel: PM3_VeryStrong, PP4_Moderate, PP3, PM2_Supporting. Classification approved by the ClinGen LSD VCEP on May 16, 2022.

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005441 (1/18378 alleles) in the East Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.98 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate	✔	At least 12 patients with this variant have been reported including 7 with documented GAA deficiency with <1% of normal mean control level of GAA activity in cultured fibroblasts or GAA activity in the affected leukocytes or dried blood spot (PMID: 22538254, 22521436, 31875618, Clinical Laboratory data), one noted to have deficient GAA activity but results were not provided (PMID: 28394184), and two reported to have Pompe disease with no further details (PMID: 26693141). At least three of these patients are receiving enzyme replacement therapy (PMID: 22521436, 22538254, 26693141 29289479, 30214072, 31899940) (PP4_Moderate).
PM3_Very Strong	✔	Of these at least 12 individuals reported with Pompe disease and this variant, at least 3 are homozygous (PMID: 22521436, 22538254, 26693141 29289479, 31899940, Clinical Laboratory data (Maximum points allowed = 2 x 0.5 = 1 point), and six were compound heterozygous for the variant and a pathogenic variant including c.1309C>T (p.Arg437Cys) phase unknown; 0.5 points) (PMID: 22521436), c.-32-13T>G (pathogenic variant) (Clinical Laboratory

Data) (phase unknown, 0.5 points), c.2608C>T (p.Arg870Ter) (Clinical Laboratory Data) (phase unknown, 0.5 points), c.525delT (PMID: 30214072) (phase unknown, 0.5 points), and c.1822C>T (p.Arg608Ter)(PMID: 31875618; confirmed in trans by parental testing; 1 point). Another individuals is compound heterozygous for the variant and and c.1118T>G (p.Leu373Arg) but the allelic data from this patient will be used in the classification of p.Leu373Arg and is not included here to avoid circular logic. Total 4 points (PM3_VeryStrong).

Not Met criteria codes

PM5	✖	Two other missense variants, c.2297A>G (p.Tyr766Cys) and 2296T>A (p.Tyr766Asn), in the same codon have been reported in patients with Pompe disease. The classification of c.2297A>C (p.Tyr766Ser) will be used to apply PM5 for those other variants and is not included here to avoid circular logic.

Curation History

Showing 1 to 1 of 1 rows

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