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Variant: NM_000152.5(GAA):c.2104C>T (p.Arg702Cys)

Version: 1.0

CA274304

189040 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6a83fe50-961a-48e8-bc45-cd557a9acfb7
Approved on: 2025/1/11
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HGVS expressions

NM_000152.5(GAA):c.2104C>T (p.Arg702Cys)
NM_000152.5:c.2104C>T
NC_000017.11:g.80113281C>T
CM000679.2:g.80113281C>T
NC_000017.10:g.78087080C>T
CM000679.1:g.78087080C>T
NC_000017.9:g.75701675C>T
NG_009822.1:g.16726C>T
ENST00000570803.6:c.2104C>T
ENST00000572080.2:c.*242C>T
ENST00000577106.6:c.2104C>T
ENST00000302262.8:c.2104C>T
ENST00000302262.7:c.2104C>T
ENST00000390015.7:c.2104C>T
ENST00000572080.1:c.523C>T
NM_000152.3:c.2104C>T
NM_001079803.1:c.2104C>T
NM_001079804.1:c.2104C>T
NM_000152.4:c.2104C>T
NM_001079803.2:c.2104C>T
NM_001079804.2:c.2104C>T
NM_001079803.3:c.2104C>T
NM_001079804.3:c.2104C>T

Pathogenic

Met criteria codes 6

PP3 PM5 PP4_Moderate PM3_Strong PM2_Supporting PS3_Supporting

Evidence Links 2

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.2104C>T variant in GAA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 702 (p.Arg702Cys). At least 1 patient with this variant had documented GAA deficiency with <30% of normal mean control level of GAA activity in cultured fibroblasts (PMID: 14972326). At least 1 patient with this variant was reported to be on enzyme replacement therapy for Pompe disease (PMID: 25687148). Other patients with this variant who were noted to have Pompe disease were found in the literature, but enzyme activity was not discussed (PMID: 20308911, 31086307) (PP4_Moderate). This variant has been detected in at least 5 individuals with Pompe disease. Of those individuals, 2 were compound heterozygous for the variant and -32-13T>G a pathogenic variant by the ClinGen Lysosomal Diseases VCEP (phase unknown)(PMID: 20308911, 24158270) and 1 individual was compound heterozygous for the variant and c.2481+110_2646+39del (confirmed in trans by parental/family testing)(PMID: 14972326). Two individuals were homozygous for the variant (PMID: 25687148, 31086307), meetings the criteria for PM3_Strong. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00004 (1/254192 alleles) in the African population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in COS resulted in less than 2% wild type GAA activity and evidence of abnormal GAA synthesis and processing, indicating that this variant may impact protein function (PMID: 14972326, 19862843)(PS3_Supporting). The computational predictor REVEL gives a score of 0.985 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Two different missense variants [c.2105G>T (p.Arg702Leu, ClinVar Variation ID: 92472) and c.2105G>A (p.Arg702His, ClinVar Variation ID: 426278)], in the same codon have been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 189040). 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 (Specifications Version 2.0): PP4_Moderate, PM3_Strong, PM2_Supporting, PS3_Supporting, PP3, PM5. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on January 11, 2025)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.985 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM5	✔	Two different missense variants [c.2105G>T (p.Arg702Leu, ClinVar Variation ID: 92472) and c.2105G>A (p.Arg702His, ClinVar Variation ID: 426278)], in the same codon have been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5).
PP4_Moderate	✔	At least 1 patient with this variant had documented GAA deficiency with <30% of normal mean control level of GAA activity in cultured fibroblasts (PMID: 14972326). At least 1 patient with this variant was reported to be on enzyme replacement therapy for Pompe disease (PMID: 25687148). Other patients with this variant who were noted to have Pompe disease were found in the literature, but enzyme activity was not discussed (PMID: 20308911, 31086307). (PP4_Moderate).
PM3_Strong	✔	This variant has been detected in at least 5 individuals with Pompe disease. Of those individuals, 2 were compound heterozygous for the variant and -32-13T>G, a pathogenic variant (not confirmed in trans), 0.5 points each (PMID: 20308911, 24158270) and 1 individual was compound heterozygous for the variant and c.2481+110_2646+39del (confirmed in trans by parental/family testing), 1 point (PMID: 14972326). Two individuals were homozygous for the variant (PMID: 25687148, 31086307), 0.5 point each. Three total points for PM3 meetings the criteria for PM3_Strong.
PM2_Supporting	✔	

The highest population minor allele frequency in gnomAD v2.1.1 is 0.00004 (1/22360 alleles) and in v4.1.0 is 0.00002 (2/74680 alleles) in the African population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

PS3_Supporting ✔

Expression of the variant in COS resulted in less than 2% wild type GAA activity and evidence of abnormal GAA synthesis and processing, indicating that this variant may impact protein function (PMID: 14972326, 19862843) (PS3_Supporting).

Table 3 lists R702C as a GAA variant with less than 2% wild type GAA activity (not bolded). "Initial GAA activity from COS-7 cells transiently transfected with mutant GAA plasmids. GAA activity was determined as described in Materials and Methods after incubation with 100mM DNJ for 48 or 72 hr. GAA variants showing mature GAA species on immunoblots are in bold. The biochemical data reported in this table was compiled from two or more independent transfections." PubMed:19862843

In vitro expression assay demonstrated no catalytic activity and western blot showed on the 110 kDa precursor. PubMed:14972326

Curation History

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