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Variant: NM_000152.5(GAA):c.265C>T (p.Arg89Cys)

Version: 1.0

CA8814832

456412 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 45d0a02d-2e8b-46dc-9a93-0b6f075b6e87
Approved on: 2023/1/2
Published on: 2023/1/2

HGVS expressions

NM_000152.5(GAA):c.265C>T (p.Arg89Cys)
NM_000152.5:c.265C>T
NC_000017.11:g.80104851C>T
CM000679.2:g.80104851C>T
NC_000017.10:g.78078650C>T
CM000679.1:g.78078650C>T
NC_000017.9:g.75693245C>T
NG_009822.1:g.8296C>T
ENST00000570803.6:c.265C>T
ENST00000572080.2:c.265C>T
ENST00000577106.6:c.265C>T
ENST00000302262.8:c.265C>T
ENST00000302262.7:c.265C>T
ENST00000390015.7:c.265C>T
ENST00000570803.5:c.265C>T
ENST00000577106.5:c.265C>T
NM_000152.3:c.265C>T
NM_001079803.1:c.265C>T
NM_001079804.1:c.265C>T
NM_000152.4:c.265C>T
NM_001079803.2:c.265C>T
NM_001079804.2:c.265C>T
NM_001079803.3:c.265C>T
NM_001079804.3:c.265C>T

Uncertain Significance

Met criteria codes 1

PP3

Not Met criteria codes 5

PM2 PM3 PM5 BS1 PP4

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.265C>T variant in GAA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 89 (p.Arg89Cys). At least 1 proband with this variant had documented GAA deficiency with activity in the affected range in dried blood spot was reported (clinical laboratory data). The patient is heterozygous for the pseudodeficiency variant(s) c.271G>A (p.Asp91Asn) and therefore the GAA activity cannot be used for PP4. The proband is compound heterozygous for the variant and a variant classified as Pathogenic by the ClinGen LSD VCEP, c.307T>G (p.Cys103Gly); the variants are confirmed in trans by parental testing. However, the phase of the pseudodeficiency variant is unknown so PM3 was not applied. The highest population minor allele frequency for this variant in gnomAD v2.1.1 is 0.001898 (58/30556 alleles) in the South Asian population (none of the population data codes are met). The computational predictor REVEL gives a score of 0.861 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). One other missense variant, c.266G>A (p.Arg89His) (ClinVar Variation ID: 283219) has been reported in patients with Pompe disease (PMID: 28196920, 28600779, 25626711, 33202836). However, this variant has been classified as a variant of uncertain significance by the ClinGen LSD VCEP and, therefore, this evidence is not sufficient to meet PM5 at any strength. There is a ClinVar entry for this variant (Variation ID: 456412; 1 star review status) with one submitter classifying the variant as Likely Pathogenic and 5 as a variant of uncertain significance. In summary, this variant meets the criteria to be classified as a Variant of Uncertain Significance for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Storage Disorders Variant Curation Expert panel (specifications Version 2.0): PP3. (Classification approved by the ClinGen LSD VCEP on December 20, 2022)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.861 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PM2	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.001898 (58/30556 alleles) in the South Asian population (none of the population data codes are met).
PM3	✖	This variant has been detected in 1 individual with Pompe disease. The individual was compound heterozygous for the variant and a pathogenic or likely pathogenic variant- c.307T>G (p.Cys103Gly)- and was confirmed in trans by parental testing. However, However, a pseudodeficiency allele, c.271G>A is present, phase unknown.
PM5	✖	One other missense variant, c.266G>A (p.Arg89His) (ClinVar Variation ID: 283219) has been reported in patients with Pompe disease (PMID: 28196920, 28600779, 25626711, 33202836). However, this variant has been classified as a variant of uncertain significance by the ClinGen LSD VCEP and, therefore, this evidence is not sufficient to meet PM5 at any strength.
BS1	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.001898 (58/30556 alleles) in the South Asian population (none of the population data codes are met).
PP4	✖	At least 1 patient(s) with this variant had documented GAA deficiency with activity in the affected range in dried blood spot was reported (Duke). The patient is heterozygous for the pseudodeficiency variant(s) c.271G>A

(p.Asp91Asn) and therefore the GAA activity cannot be used for PP4.

Curation History

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