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Variant: NM_000152.3(GAA):c.307T>G (p.Cys103Gly)

Version: 1.0

CA220404

92483 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: e5afb18d-a245-421a-9d32-466c06f390cf
Approved on: 2022/9/21
Published on: 2022/10/21

HGVS expressions

NM_000152.3(GAA):c.307T>G (p.Cys103Gly)
NM_000152.3:c.307T>G
NC_000017.11:g.80104893T>G
CM000679.2:g.80104893T>G
NC_000017.10:g.78078692T>G
CM000679.1:g.78078692T>G
NC_000017.9:g.75693287T>G
NG_009822.1:g.8338T>G
ENST00000570803.6:c.307T>G
ENST00000572080.2:c.307T>G
ENST00000577106.6:c.307T>G
ENST00000302262.8:c.307T>G
ENST00000302262.7:c.307T>G
ENST00000390015.7:c.307T>G
ENST00000570803.5:c.307T>G
ENST00000577106.5:c.307T>G
NM_001079803.1:c.307T>G
NM_001079804.1:c.307T>G
NM_000152.4:c.307T>G
NM_001079803.2:c.307T>G
NM_001079804.2:c.307T>G
NM_000152.5:c.307T>G
NM_001079803.3:c.307T>G
NM_001079804.3:c.307T>G

Pathogenic

Met criteria codes 5

PP3 PP4_Moderate PM3_Strong PM2_Supporting PS3_Moderate

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.307T>G variant in GAA is a missense variant predicted to cause substitution of cysteine by glycine at amino acid 103 (p.Cys103Gly). This variant has been reported in at least 12 patients who have been diagnosed with Pompe disease, including patients with documented GAA deficiency in the affected range in dried blood spot, leukocytes, and fibroblasts and <10% normal GAA activity in muscle (PMIDs: 16838077, 18285536, 21109266, 22676651, 24011652, 24158270, 29803406; Pediatr Pol 2021; 96 (3): 220–222; https://doi.org/10.5114/polp.2021.109310) and three on enzyme replacement therapy (PMID: 18607768, 29565424, 29803406, 23160972) (PP4_Moderate). Of note, in some of these patients, the variant was noted to be in cis with another variant (p.Asp91Asn) which can falsely lower GAA activity in in vitro assays when the substrate is glycogen, but not when the substrate is an artificial substrate, 4-MU. This was taken into account when utilizing GAA activity data. Of the reported patients, at least 11 patients compound heterozygous for the variant, phase unknown, and a known pathogenic variant in GAA including c.-32-13T>G (9 patients, PMID: 16838077, 18285536, 18607768, 21109266, 22676651, 23160972, 24011652, 24158270, 29803406; Pediatr Pol 2021; 96 (3): 220–222; https://doi.org/10.5114/polp.2021.109310), c.525delT (PMID: 14695532) and c.2481+102_c.2646+31del (PMID: 29565424). In addition, one patient is compound heterozygous for the variant and c.1465G>A (p.Asp489Asn) (PMID: 18429042). The allelic data from this patient will be used in the assessment of p.Asp489Asn and is not included here to avoid circular logic. For another patient, the cDNA change for the variants was not provided and therefore the data was not included (PMID: 28196920). The highest population minor allele frequency in gnomAD is 0.00001 (1/126998 alleles) in the European non-Finnish population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). When expressed in COS cells, the variant resulted in 1.5% normal activity, and evidence of abnormal GAA processing on Western blot (PMID: 14695532) (PS3_Moderate). 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 other amino acid substitutions at the same position have been reported in patients with Pompe disease - c.307T>C (p.Cys103Arg) (PMIDs 21984055, 22644586) and c.309C>G (p.Cys103Trp) (PMID 27142047); the classification of p.Cys103Gly will be used to support the classification of these other variants. Therefore, the data is not used here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 92483, 2 star review status) with 8 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. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PM3_Strong, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Approved by the ClinGen LSD VCEP on Sept. 21, 2022).

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).
PP4_Moderate	✔	This variant has been reported in at least 12 patients who have been diagnosed with Pompe disease, including patients with documented GAA deficiency in the affected range in dried blood spot, leukocytes, and fibroblasts and <10% normal GAA activity in muscle (PMIDs: 16838077, 18285536, 21109266, 22676651, 24011652, 24158270, 29803406; Pediatr Pol 2021; 96 (3): 220–222; https://doi.org/10.5114/polp.2021.109310) and three on enzyme replacement therapy (PMID: 18607768, 29565424, 29803406, 23160972) (PP4_Moderate). Of note, in some of these patients, the variant was noted to be in cis with a variant (p.Asp91Asn) which can result in false positive GAA deficiency when GAA activity is measured with glycogen but not when measured with the artificial substrate, 4-MU (PMID 33162552). This was taken into account when utilizing GAA activity data.
PM3_Strong	✔	At least 11 patients are compound heterozygous for the variant and a known pathogenic variant in GAA including c.-32-13T>G (9 patients, PMID: 16838077, 18285536, 18607768, 21109266, 22676651, 23160972, 24011652, 24158270, 29803406; Pediatr Pol 2021; 96 (3): 220–222; https://doi.org/10.5114/polp.2021.109310) (maximum of 2 x 0.5 points), c.525delT (PMID: 14695532) (phase unknown, 0.5 points), and c.2481+102_c.2646+31del (PMID:

29565424) (phase unknown, 0.5 points). Total points = 2 (PM3_STrong) In addition, one patient is compound heterozygous for the variant and c.1465G>A (p.Asp489Asn) (PMID: 18429042). The allelic data from this patient will be used in the assessment of p.Asp489Asn and is not included here to avoid circular logic. For another patient, the cDNA change for the variants was not provided and therefore the data was not included (PMID: 28196920).

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD is 0.00001 (1/126998 alleles) in the European non-Finnish population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PS3_Moderate	✔	When expressed in COS cells, the variant resulted in 1.5% normal activity, and evidence of abnormal GAA processing on Western blot (PMID: 14695532) (PS3_Moderate).

Not Met criteria codes

PM5	✖	Two other variants have been reported at the same amino acid position in patients with Pompe disease; c.307T>C (p.Cys103Arg) (PMIDs 21984055, 22644586) and c.309C>G (p.Cys103Trp) (PMID 27142047). This data will be used to support the classification of these variants and is not included here in order to avoid circular logic.

Curation History

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