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Variant: NM_000152.5(GAA):c.2105G>A (p.Arg702His)

Version: 1.0

CA8815610

426278 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 15c8deda-d3b2-4e03-a4c6-3c97f3b96012
Approved on: 2024/3/5
Published on: 2024/3/26

HGVS expressions

NM_000152.5(GAA):c.2105G>A (p.Arg702His)
NM_000152.5:c.2105G>A
NC_000017.11:g.80113282G>A
CM000679.2:g.80113282G>A
NC_000017.10:g.78087081G>A
CM000679.1:g.78087081G>A
NC_000017.9:g.75701676G>A
NG_009822.1:g.16727G>A
ENST00000570803.6:c.2105G>A
ENST00000572080.2:c.*243G>A
ENST00000577106.6:c.2105G>A
ENST00000302262.8:c.2105G>A
ENST00000302262.7:c.2105G>A
ENST00000390015.7:c.2105G>A
ENST00000572080.1:c.524G>A
NM_000152.3:c.2105G>A
NM_001079803.1:c.2105G>A
NM_001079804.1:c.2105G>A
NM_000152.4:c.2105G>A
NM_001079803.2:c.2105G>A
NM_001079804.2:c.2105G>A
NM_001079803.3:c.2105G>A
NM_001079804.3:c.2105G>A

Pathogenic

Met criteria codes 6

PS3_Supporting PP4_Moderate PM3_Strong PM2_Supporting PM5 PP3

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.2105G>A variant in GAA is a missense variant predicted to cause substitution of arginine by histidine at amino acid 702 (p.Arg702His). At least 3 unrelated patients were noted to have deficient GAA activity but results were not provided (PMID: 26310554, 30897595, 28394184). Two patients are described as having IOPD with clinical symptoms consistent with IOPD reported in one (PMID: 26310554). One patient is described as having juvenile-onset Pompe disease with deficient GAA (value not provided) (PMID: 18211760). Another patient is reported to have deficient GAA and late-onset Pompe disease (PMID: 30897595) (PP4_Moderate). At least one patient is described as having this variant in trans with a variant classified as likely pathogenic by the ClinGen Lysosomal Diseases (LD) VCEP (c.796C>T, p.Pro266Ser; ClinVar Variation ID Variation ID: 556117; SCV002540664.1) (PMID: 18211760). At least two patients have been reported with this variant in compound heterozygosity with another variant that has been classified as pathogenic by the ClinGen LD VCEP (c.2297A>C, p.Tyr766Ser, ClinVar Variation ID: Variation ID: 420102, SCV002540647.1, and c.2238G>C, p.Trp746Cys, ClinVar Variation ID: Variation ID: 265160, SCV002032122.1), phase unconfirmed for both (PMID: 28394184 and 30897595) (PM3_Strong). This variant is absent in gnomAD v2.1.1. (PM2_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). Expression of the variant in COS-7 cells resulted in 5% wild type GAA activity in medium and 13% residual activity in cells with evidence of abnormal synthesizing and processing (PMID: 18425781) leading the variant to be described as Class D “potentially mild” indicating that this variant may impact protein function (PS3_supporting). Another missense variant (c.2105G>T, p.Arg702Leu) in the same codon has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP (ClinVar Variation ID: Variation ID: 92472)(PM5). There is a ClinVar entry for this variant (Variation ID: 426278). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3_strong, PM5, PP4_moderate, PM2_supporting, PP3, PS3_supporting.

Met criteria codes

PS3_Supporting	✔	Expression of the variant in COS-7 cells resulted in 5% wild type GAA activity in medium and 13% residual activity in cells with evidence of abnormal synthesizing and processing (Kroos et al, 2008 PMID: 18425781) – leading the variant to be described as Class D “potentially mild” indicating that this variant may impact protein function (PS3_supporting).
PP4_Moderate	✔	At least 3 unrelated patients were noted to have deficient GAA activity but results were not provided (PMID: 26310554, 30897595, 28394184). Two patients are described as having IOPD with clinical symptoms consistent with IOPD reported in one (PMID: 26310554) (PP4). One patient is described as having juvenile-onset Pompe disease with deficient GAA (value not provided) (PMID: 18211760). Another patient is reported to have deficient GAA and late-onset Pompe disease (PMID: 30897595) (PP4_Moderate).
PM3_Strong	✔	At least one patient is described as having this variant in trans with a variant classified as likely pathogenic by the ClinGen LD VCEP (c.796C>T, p.Pro266Ser; ClinVar Variation ID Variation ID: 556117; SCV002540664.1) (PMID: 18211760) (1 point). At least two patients have been reported with this variant in compound heterozygosity with another variant that has been classified as pathogenic by the ClinGen LD VCEP (c.2297A>C, p.Tyr766Ser, ClinVar Variation ID: Variation ID: 420102, SCV002540647.1, and c.2238G>C, p.Trp746Cys, ClinVar Variation ID: Variation ID: 265160, SCV002032122.1, phase unconfirmed (PMID: 28394184 and 30897595) (2 x 0.5 points). Total 2 points (PM3_Strong).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1. (PM2_Supporting). // The highest population minor allele frequency in gnomAD v4.0. is 0.0003 (2/6058 alleles) in the Middle Eastern population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

PM5		✔	Another missense variant [c.2105G>T, p.Arg702Leu] in the same codon has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (ClinVar Variation ID: Variation ID: 92472) (PM5).
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).

Curation History

Showing 1 to 1 of 1 rows

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