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Variant: NM_000152.4(GAA):c.1478C>T (p.Pro493Leu)

Version: 1.1

CA16608675

379593 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 74ca2bbb-1318-49e8-9e55-889570530623
Approved on: 2024/7/21
Published on: 2024/9/17

HGVS expressions

NM_000152.4:c.1478C>T
NM_000152.4(GAA):c.1478C>T (p.Pro493Leu)
NC_000017.11:g.80110767C>T
CM000679.2:g.80110767C>T
NC_000017.10:g.78084566C>T
CM000679.1:g.78084566C>T
NC_000017.9:g.75699161C>T
NG_009822.1:g.14212C>T
ENST00000570803.6:c.1478C>T
ENST00000572080.2:c.1478C>T
ENST00000577106.6:c.1478C>T
ENST00000302262.8:c.1478C>T
ENST00000302262.7:c.1478C>T
ENST00000390015.7:c.1478C>T
NM_000152.3:c.1478C>T
NM_001079803.1:c.1478C>T
NM_001079804.1:c.1478C>T
NM_001079803.2:c.1478C>T
NM_001079804.2:c.1478C>T
NM_000152.5:c.1478C>T
NM_001079803.3:c.1478C>T
NM_001079804.3:c.1478C>T

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM3_Strong PM2_Supporting 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.1478C>T variant in GAA is predicted to result in the substitution of proline by leucine at amino acid 493 (p.Pro493Leu). At least 7 probands have been reported with this variant, including one adult and an affected sibling with documented values showing GAA activity below the normal range on dried blood spot assay, and treated with enzyme replacement therapy (ERT) (PMID 24495340), and another four individuals with features consistent with Pompe disease, three of them on enzyme replacement therapy (PMID: 25455803, 29181627, 31545528, 33188503). Furthermore, three individuals with the same genotype (thought to be unrelated but cannot be confirmed) were identified in a clinical diagnostic laboratory with GAA activity below the normal range on dried blood spot (PP4_Moderate). Two additional patients have been reported with P493L, but the cDNA change was not provided and, one patient was heterozygous without the identification of a second variant, therefore, this data will not be included (PMID: 20033296, 23160972, 31545528), and patient with suspected late onset Pompe disease was identified by newborn screening but was asymptomatic (PMID: 33202836). The 7 probands are compound heterozygous for the variant and a variant that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP. The phase is unconfirmed in all of these patients. The second variant is either c.525delT (PMID: 25455803, and 3 presumably unrelated patients identified by a clinical diagnostic laboratory, max 2 patients counted, ClinVar Variation ID: 4033, SCV001443331.1; 2 x 0.5 points), c.1134C>G (p.Tyr378Ter), phase unknown (PMID: 29181627, ClinVar Variation ID: 595469, SCV001443283.2, 0.5 points), c.307T>G (p.Cys103Gly) (PMID: 24495340, ClinVar Variation ID: 92483, SCV002817442.1, 0.5 points), c.2560C>T (p.Arg854Ter) (ClinVar Variation ID: 4034, SCV001371731.1, 0.5 points), c.1655T>C (p.Leu552Pro) (PMID: 31545528, ClinVar Variation ID: 279811, SCV001371750.2) or c.-32-13T>G (PMID: 33188503, ClinVar Variation ID: 4027). 7 x 0.5 points = 3.5 points (PM3_Strong). The highest population minor allele frequency (MAF) in gnomAD v2.1.1 is 0.00003 (4/128962 alleles) in the European non-Finnish population, and in gnomAD v4.1. the MAF is 0.00001695 (20/1180038) in the European non-Finnish population. Both are lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.911 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). To our knowledge, results of functional studies are not available for this variant. There is a ClinVar entry for this variant (Variation ID 379593). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3_Strong, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on July 21, 2024)

Met criteria codes

PP4_Moderate	✔	Two adult siblings have been reported with documented values showing GAA activity below the normal range on dried blood spot assay, and treated with enzyme replacement therapy (ERT) (PMID 24495340), and another three individuals have been reported with features consistent with Pompe disease, three of them were on ERT (PMID: 25455803, 29181627, 31545528). Four individuals were identified in a clinical diagnostic laboratory with GAA activity below the normal range on dried blood spot (PP4_Moderate). A patient with suspected late onset Pompe disease was identified by newborn screening (PMID: 33202836). In addition, two patients have been reported with P493L, but the cDNA change was not provided and, one patient was heterozygous without the identification of a second variant, therefore, this data will not be included (PMID: 20033296, 23160972, 31545528).
PM3_Strong	✔	At least 7 probands have been reported who are compound heterozygous for the variant and a variant that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP. The phase is unconfirmed in all of these patients. The second variant is either c.525delT (PMID: 25455803, and 3 presumably unrelated patients identified by a clinical diagnostic laboratory, max 2 patients counted, ClinVar Variation ID: 4033, SCV001443331.1; 2 x 0.5 points), c.1134C>G (p.Tyr378Ter), phase unknown (PMID: 29181627, ClinVar Variation ID: 595469, SCV001443283.2, 0.5 points), c.307T>G (p.Cys103Gly) (PMID: 24495340, ClinVar Variation ID: 92483, SCV002817442.1, 0.5 points), c.2560C>T (p.Arg854Ter) (ClinVar Variation ID: 4034, SCV001371731.1, 0.5 points), c.1655T>C (p.Leu552Pro) (PMID: 31545528, ClinVar Variation ID: 279811, SCV001371750.2) or c.-32-13T>G (PMID: 33188503, ClinVar Variation ID: 4027). 7 x 0.5 points = 3.5 points (PM3_Strong)

PM2_Supporting		✔	The highest population minor allele frequency (MAF) in gnomAD v2.1.1 is 0.00003 (4/128962 alleles) in the European non-Finnish population, and in gnomAD v4.1. the MAF is 0.00001695 (20/1180038) in the European non-Finnish population. Both are lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	ℹ	✔	The computational predictor REVEL gives a score of 0.911 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Curation History

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