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Variant: NM_000152.5(GAA):c.1564C>G (p.Pro522Ala)

Version: 1.0

CA16041893

371277 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 14e28913-369c-46e3-8235-50bb31d98411
Approved on: 2024/3/19
Published on: 2024/3/26

HGVS expressions

NM_000152.5(GAA):c.1564C>G (p.Pro522Ala)
NM_000152.5:c.1564C>G
NC_000017.11:g.80110953C>G
CM000679.2:g.80110953C>G
NC_000017.10:g.78084752C>G
CM000679.1:g.78084752C>G
NC_000017.9:g.75699347C>G
NG_009822.1:g.14398C>G
ENST00000570803.6:c.1564C>G
ENST00000572080.2:c.1564C>G
ENST00000577106.6:c.1564C>G
ENST00000302262.8:c.1564C>G
ENST00000302262.7:c.1564C>G
ENST00000390015.7:c.1564C>G
NM_000152.3:c.1564C>G
NM_001079803.1:c.1564C>G
NM_001079804.1:c.1564C>G
NM_000152.4:c.1564C>G
NM_001079803.2:c.1564C>G
NM_001079804.2:c.1564C>G
NM_001079803.3:c.1564C>G
NM_001079804.3:c.1564C>G

Pathogenic

Met criteria codes 6

PS3_Supporting PP4_Moderate PM3_Strong PM2_Supporting PM5_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.1564C>G variant in GAA is a missense variant predicted to cause substitution of proline by alanine at amino acid 522 (p.Pro522Ala). This variant has been detected in at least 7 unrelated patients reported to have Pompe disease including four individuals with reported laboratory values demonstrating deficient GAA activity (PMID: 26800218, 33301762, 34072668, Duke University), and three for whom GAA activity was not reported (PMID: 18429042, 37087815) (PP4_Moderate). Of those individuals, 6 were compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LD VCEP: c.784G>A (p.Glu262Lys) (ClinVar Variation ID: 188806, SCV002032128.1) (PMID: 18429042), c.1933G>A (p.Asp645Asn) (ClinVar Variation ID: 188728, SCV001371736.1) (PMID: 18429042), c.1465G>A (p.Asp489Asn) (ClinVar Variation ID: 92465, SCV003852732.1) (PMID: 34072668), and c.-32-13T>G (ClinVar Variation ID: 4027) (PMID: 26800218, 37087815, Clinical Diagnostic Laboratory; at least 3 unrelated patients). The phase is not confirmed for any of these individuals. One individual was homozygous for this variant (PMID: 33301762) (PM3_Strong). Another missense variant, c.1564C>T, p.Pro522Ser (ClinVar Variation ID: 972746) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_Supporting). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). Expression of the variant in Ad5-SV40 immortalized human GAA-deficient fibroblast cell line resulted in 0% wild type GAA activity when measured using fluorogenic substrate 4-methylumbelliferyl-α-D glucopyranoside. This was further supported via Western blot analysis demonstrating deficient GAA protein expression (PMID: 18429042) (PS3_Supporting). The computational predictor REVEL gives a score of 0.883 which is above the threshold predicting a damaging (>0.7) impact on GAA function. There is a ClinVar entry for this variant (Variation ID: 371277). 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): PM3_Strong, PP4_Moderate, PM2_Supporting, PM5_Supporting PS3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on March 19, 2024).

Met criteria codes

PS3_Supporting	✔	Expression of the variant in Ad5-SV40 immortalized human GAA-deficient fibroblast cell line resulted in 0% wild type GAA activity when measured using fluorogenic substrate 4-methylumbelliferyl-α-D glucopyranoside. This was further supported via Western blot analysis demonstrating deficient GAA protein expression (PMID: 18429042) (PS3_Supporting).
PP4_Moderate	✔	This variant has been detected in at least 7 unrelated patients reported to have Pompe disease including four individuals with reported laboratory values demonstrating deficient GAA activity (PMID: 26800218, 33301762, 34072668, Duke University), and three for whom GAA activity was not reported (PMID: 18429042, 37087815) (PP4_Moderate).
PM3_Strong	✔	This variant has been detected in at least 7 unrelated individuals with Pompe disease. Of those individuals, 6 were compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LD VCEP: c.784G>A (p.Glu262Lys) (ClinVar Variation ID: 188806, SCV002032128.1) (PMID: 18429042) (0.5 points), c.1933G>A (p.Asp645Asn) (ClinVar Variation ID: 188728, SCV001371736.1) (PMID: 18429042) (0.5 points), c.1465G>A (p.Asp489Asn) (ClinVar Variation ID: 92465, SCV003852732.1) (PMID: 34072668) (0.5 points), and c.-32-13T>G (ClinVar Variation ID: 4027) (PMID: 26800218, 37087815, Clinical Diagnostic Laboratory) at least 3 unrelated patients, maximum 2 x 0.5 points). The phase is not confirmed for any of these individuals. One individual was homozygous for this variant (PMID: 33301762). (3.0 points; PM3_Strong).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1. (PM2_Supporting). The highest population minor allele frequency in gnomAD v4.0.0 is 0.000000893 (1/1111960 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

PM5_Supporting	ℹ	✔	Another missense variant, c.1564C>T, p.Pro522Ser (ClinVar Variation ID: 972746) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_Supporting).
PP3	ℹ	✔	The computational predictor REVEL gives a score of 0.883 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Curation History

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