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Variant: NM_001079804.3:c.1564C>T

Version: 1.0

CA294895008

972746 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8d0b8d64-db57-46e0-9793-2c38dcff3359
Approved on: 2024/3/19
Published on: 2024/3/26

HGVS expressions

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

Likely Pathogenic

Met criteria codes 4

PS3_Moderate PP4_Moderate PM2_Supporting PP3

Not Met criteria codes 1

PM3

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>T variant in GAA is a missense variant predicted to cause substitution of proline by serine at amino acid 522 (p.Pro522Ser). Two probands with a confirmed diagnosis of IOPD have been reported with this variant (PMID: 32518148, 38250073), both CRIM-positive, one with documented symptoms of IOPD and the other on ERT (PP4_Moderate). Both probands are compound heterozygotes for the variant and other variants that have yet to be classified by the ClinGen Lysosomal Diseases VCEP (PM3_Not Met). This variant has a minor allele frequency in gnomAD v2.1.1 of 0.00001761 in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP threshold (<0.001) for PM2, meeting this criterion. Functional assays support a deleterious effect of this variant, when expressed in COS cells, this variant was classified as Class B ("potentially less severe"). This includes 0.8% GAA activity in cells and 0.8% in medium, and evidence of abnormal synthesis and processing on Western blot (PMID: 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.932 which is higher than the ClinGen LD VCEP threshold for PP3 (>0.7) and therefore meets this criterion. There is a ClinVar entry for this variant (Variation ID: 972746). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP: PP4_Moderate, PS3_Moderate, PM2_Supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on March 19, 2024).

Met criteria codes

PS3_Moderate	✔	When expressed in COS cells, this variant results in 0.8% GAA activity in cells, and there is evidence of abnormal synthesis and processing on Western blot (PMID: 22644586). This meets the ClinGen Lysosomal Diseases VCEP's specifications for PS3_Moderate.
PP4_Moderate	✔	The variant has been detected in three patients with Pompe disease, including one patient who was CRIM-positive and a confirmed diagnosis of IOPD based on low GAA enzyme activity (PMID: 38250073). Another individual was also CRIM-positive and diagnosed with IOPD, however, individual results of GAA activity were not reported (PMID: 32518148). This variant was also seen in a patient with Pompe disease but the GAA activity was not given (PMID: 18425781) (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001761 (2/113602 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). The highest population minor allele frequency in gnomAD v4.0.0 is 0.000008475 (10/1179962 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).
PP3	✔	The computational predictor REVEL gives a score of 0.932 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PM3	✖	This variant has been detected in 2 individuals with Pompe disease. Both individuals were compound heterozygotes for the variant and a variant that has not been classified by the ClinGen LD VCEP. The phase is not confirmed for any of these individuals. One individual was homozygous for this variant (0 points; PM3_Not Met).

Curation History

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