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Variant: NM_000152.5(GAA):c.1796C>A (p.Ser599Tyr)

Version: 1.1

CA8815479

551558 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6cc7e901-48af-4d21-aa66-c5033a652c95
Approved on: 2024/11/22
Published on: 2024/12/17

HGVS expressions

NM_000152.5(GAA):c.1796C>A (p.Ser599Tyr)
NM_000152.5:c.1796C>A
NC_000017.11:g.80112619C>A
CM000679.2:g.80112619C>A
NC_000017.10:g.78086418C>A
CM000679.1:g.78086418C>A
NC_000017.9:g.75701013C>A
NG_009822.1:g.16064C>A
ENST00000570803.6:c.1796C>A
ENST00000572080.2:c.1796C>A
ENST00000577106.6:c.1796C>A
ENST00000302262.8:c.1796C>A
ENST00000302262.7:c.1796C>A
ENST00000390015.7:c.1796C>A
ENST00000570716.1:n.236C>A
ENST00000572080.1:c.184C>A
ENST00000572803.1:n.410C>A
NM_000152.3:c.1796C>A
NM_001079803.1:c.1796C>A
NM_001079804.1:c.1796C>A
NM_000152.4:c.1796C>A
NM_001079803.2:c.1796C>A
NM_001079804.2:c.1796C>A
NM_001079803.3:c.1796C>A
NM_001079804.3:c.1796C>A

Likely Pathogenic

Met criteria codes 5

PM3 PP4_Moderate PS3_Moderate PP3 PM2_Supporting

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.1796C>A variant in GAA is a missense variant predicted to cause substitution of serine by tyramine at amino acid 599 (p.Ser599Tyr). At least 4 probands have been reported with clinical symptoms consistent with Pompe, typically late onset of symptoms, and documentation of reduced enzyme activity in the affected range (PMID: 37087815 and/or on enzyme replacement therapy (PMID: 29122469, 29803406, 31710733). Additional patients have symptoms consistent with Pompe disease but no details were available on GAA activity (PMID: 32419263). At least 4 individuals are compound heterozygous, phase unconfirmed, for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP including c.-32-13T>G (at least 2 patients) (PMID: 29122469, 31710733, 32419263, 37087815) (max 2 x 0.5 points = 1 point), and c.655G>A (p.Gly219Arg) (PMID: 18429042) (0.5 points). Another individuals is compound heterozygous for the variant and c.364A>G (p.Met122Val); phase unknown (PMID: 29803406). The allelic data for the proband will be used in the assessment of p.Met122Val and is not included here to avoid circular logic. Total 1.5 points (PM3). The highest population minor allele frequency in gnomAD v2.1.0 is 0.00002683 (3/111834; no homozygotes) and in gnomAD v4.1.0 it is 0.000005932 (7/1179950; no homozygotes) in the European (non-Finnish) population, which is lower than the ClinGen LD VCEP threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in COS cells resulted in 0% wild type GAA activity and evidence of abnormal GAA synthesis and processing leading the variant to be described as Class A (“very severe”). An additional study demonstrated 0% GAA activity in Ad5-SV40 fibroblast cells and abnormal Western blot results, indicating that this variant may impact protein function (PMIDs 18425781, 18429042)(PS3_Moderate). The computational predictor REVEL gives a score of 0.974 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 551558). 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 Variant Curation Expert Panel (Specifications Version 2): PS3_Moderate, PM3, PP3, PP4_Moderate, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on November 22, 2024).

Met criteria codes

PM3	✔	At least 4 individuals are compound heterozygous, phase unconfirmed, for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP including c.-32-13T>G (at least 2 patients) (PMID: 29122469, 31710733, 32419263, 37087815) (max 2 x 0.5 points = 1 point), and c.655G>A (p.Gly219Arg) (PMID: 18429042) (0.5 points). Another individuals is compound heterozygous for the variant and c.364A>G (p.Met122Val); phase unknown (PMID: 29803406). The allelic data for the proband will be used in the assessment of p.Met122Val and is not included here to avoid circular logic. Total 1.5 points (PM3).
PP4_Moderate	✔	At least 4 probands have been reported with clinical symptoms consistent with Pompe, typically late onset of symptoms, and documentation of reduced enzyme activity in the affected range (PMID: 37087815 and/or on enzyme replacement therapy (PMID: 29122469, 29803406, 31710733). Additional patients have symptoms consistent with Pompe disease but no details were available on GAA activity (PMID: 32419263).
PS3_Moderate	✔	Expression of the variant in COS cells resulted in 0% wild type GAA activity and evidence of abnormal GAA synthesis and processing leading the variant to be described as Class A (“very severe”), indicating that this variant may impact protein function (PMIDs 18425781, 18429042)(PS3_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.974 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.0 is 0.00002683 (3/111834; no homozygotes) and in gnomAD v4.1.0 it is 0.000005932 (7/1179950; no homozygotes) in the European (non-Finnish) population, which is lower than the ClinGen LD VCEP threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Curation History

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