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Variant: NM_000152.5(GAA):c.1194+3G>C

Version: 1.0

CA247031

198393 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4d1ae9e6-ee32-4e9d-b802-71c188a8ca78
Approved on: 2022-12-06
Published on: 2022-12-20

HGVS expressions

NM_000152.5:c.1194+3G>C
NM_000152.5(GAA):c.1194+3G>C
NC_000017.11:g.80108610G>C
CM000679.2:g.80108610G>C
NC_000017.10:g.78082409G>C
CM000679.1:g.78082409G>C
NC_000017.9:g.75697004G>C
NG_009822.1:g.12055G>C
ENST00000570803.6:c.1194+3G>C
ENST00000572080.2:c.1194+3G>C
ENST00000577106.6:c.1194+3G>C
ENST00000302262.8:c.1194+3G>C
ENST00000302262.7:c.1194+3G>C
ENST00000390015.7:c.1194+3G>C
NM_000152.3:c.1194+3G>C
NM_001079803.1:c.1194+3G>C
NM_001079804.1:c.1194+3G>C
NM_000152.4:c.1194+3G>C
NM_001079803.2:c.1194+3G>C
NM_001079804.2:c.1194+3G>C
NM_001079803.3:c.1194+3G>C
NM_001079804.3:c.1194+3G>C

Likely Pathogenic

Met criteria codes 3

PP4_Moderate PM3_Strong PM2_Supporting

Not Met criteria codes 1

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.1194+3G>C variant in GAA is located in the donor splice site consensus region of intron 7. The variant has been identified in three patients, all with documented laboratory values showing deficient GAA activity (Clinical Diagnostic Laboratories, PMID: 33073003) (PP4_Moderate). All of these patients are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP, including c.1781G>A (p.Arg594His), LP (mother is heterozygous for c.1781G>A, no paternal testing), (Clinical Laboratory, PMID: 33073003); c.1210G>A (p.Asp404Asn), confirmed in trans (Clinical Laboratory), and c.1841C>A (p.Thr614Lys), phase unknown,(Clinical Laboratory (PM3_Strong). The computational predictor SpliceAI does not predict a strong impact on splicing (all scores<0.2). However, varSEAK classifies that variant as having a splicing effect (class 5). There is a ClinVar entry for this variant (Variation ID: 198393). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG-AMP criteria met, as specified by the ClinGen Lysosomal Storage Disorders VCEP (Specifications Version 2.0): PM3_Strong, PP4_Moderate, PM2_Supporting. (Classification approved by the ClinGen LSD VCEP on December 6, 2022)

Met criteria codes

PP4_Moderate	✔	The variant has been identified in three patients, all with documented laboratory values showing deficient GAA activity (Clinical Diagnostic Laboratories, PMID: 33073003) (PP4_Moderate).
PM3_Strong	✔	Three patients have been reported who are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP, including c.1781G>A (p.Arg594His), LP (mother is heterozygous for c.1781G>A, no paternal testing), 0.5 points (Clinical Laboratory, PMID: 33073003); c.1210G>A (p.Asp404Asn), confirmed in trans, 1 point (Clinical Laboratory), and c.1841C>A (p.Thr614Lys), phase unknown, 0.5 points (Clinical Laboratory. Total 2 points (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00031 (40/127034 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PP3	✖	The computational predictor SpliceAI does not predict a strong impact on splicing (all scores<0.2). However, varSEAK classifies that variant as having a splicing effect (class 5).

Curation History

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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.