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Variant: NM_000152.5:c.399C>A

Version: 1.2

CA401361056

932906 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 31db1a86-3a2d-4b40-ad3e-b72a3a3e4511
Approved on: 2020/2/14
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HGVS expressions

NM_000152.5:c.399C>A
NC_000017.11:g.80104985C>A
CM000679.2:g.80104985C>A
NC_000017.10:g.78078784C>A
CM000679.1:g.78078784C>A
NC_000017.9:g.75693379C>A
NG_009822.1:g.8430C>A
ENST00000570803.6:c.399C>A
ENST00000572080.2:c.399C>A
ENST00000577106.6:c.399C>A
ENST00000302262.8:c.399C>A
ENST00000302262.7:c.399C>A
ENST00000390015.7:c.399C>A
ENST00000570803.5:c.399C>A
ENST00000577106.5:c.399C>A
NM_000152.3:c.399C>A
NM_001079803.1:c.399C>A
NM_001079804.1:c.399C>A
NM_000152.4:c.399C>A
NM_001079803.2:c.399C>A
NM_001079804.2:c.399C>A
NM_001079803.3:c.399C>A
NM_001079804.3:c.399C>A

Pathogenic

Met criteria codes 4

PM3_Supporting PP4 PM2 PVS1

Evidence Links 1

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.399C>A (p.Tyr133Ter), is a nonsense variant that is predicted to result in nonsense mediated decay and absence of gene product, meeting PVS1. When expressed in COS-1 cells, the variant results in no GAA activity and the mutant protein cannot be detected on Western blot, (PMID 14972326) supporting that it is a loss of function variant. The variant is absent in gnomAD v2.1.1, meeting PM2. A patient with infantile onset Pompe disease meeting the ClinGen LSD VCEP's specifications for PP4 has been reported who is homozygous for the variant; both parents were confirmed to be heterozygotes (PMID 14972326), meeting PM3_Supporting. There is no ClinVar entry for this varint. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PVS1, PM2, PM3_Supporting, PP4.

Met criteria codes

PM3_Supporting	✔	A patient with infantile onset Pompe disease and no detectable GAA activity in cultured fibroblasts (meeting PP4) was reported to be homozygous for this variant; both parents were confirmed to be heterozygotes (PMID 14972326). Based on the ClinGen LSD VCEP's specifications, this data was given a total of 0.5 points, which meets PM3_Supporting. Proband 1 has infantile onset Pompe disease and is homozygous for c.399C>A (p.Tyr133X*); both parents are confirmed to be heterozygous for the variant. The patient has no detectable GAA activity in cultured fibroblasts (PMID 14972326), meeting PP4. This data was awarded 0.5 points based on the specifications of the ClinGen LSD VCEP. PubMed:14972326
PP4	✔	Proband 1 has infantile onset Pompe disease and was reported who is homozygous for this variant. She has no detectable GAA activity in cultured fibroblasts (PMID 14972326). This meets the specifications for PP4. Proband 1 is homozygous for the variant and has absent GAA activity in cultured fibroblasts. PubMed:14972326
PM2	✔	This variant is not in gnomAD v2.1.1.
PVS1	✔	This is a nonsense variant which is predicted to cause nonsense mediated decay resulting in no gene product. Therefore, PVS1 can be applied.

Curation History

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