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Variant: NM_000152.4(GAA):c.573C>A (p.Tyr191Ter)

Version: 1.0

CA16041885

370276 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 08e9886c-b096-4ec6-ac73-d3614d005d8a
Approved on: 2020/5/19
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HGVS expressions

NM_000152.4(GAA):c.573C>A (p.Tyr191Ter)
NM_000152.4:c.573C>A
NC_000017.11:g.80105775C>A
CM000679.2:g.80105775C>A
NC_000017.10:g.78079574C>A
CM000679.1:g.78079574C>A
NC_000017.9:g.75694169C>A
NG_009822.1:g.9220C>A
ENST00000570803.6:c.573C>A
ENST00000572080.2:c.573C>A
ENST00000577106.6:c.573C>A
ENST00000302262.8:c.573C>A
ENST00000302262.7:c.573C>A
ENST00000390015.7:c.573C>A
ENST00000570803.5:c.573C>A
ENST00000577106.5:c.573C>A
NM_000152.3:c.573C>A
NM_001079803.1:c.573C>A
NM_001079804.1:c.573C>A
NM_001079803.2:c.573C>A
NM_001079804.2:c.573C>A
NM_000152.5:c.573C>A
NM_001079803.3:c.573C>A
NM_001079804.3:c.573C>A

Pathogenic

Met criteria codes 3

PM2 PVS1 PP4

Not Met criteria codes 1

PM3

Evidence Links 3

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.573C>A (p.Tyr191Ter), is a nonsense variant that is predicted to result in nonsense-mediated decay and lack of gene product, meeting PVS1. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 in the Latino population, meeting PM2. Two patients meeting the ClinGen LSD VCEP's specifications for PP4 have been reported. These patients are compound heterozygous for the variant and either c.2173C>T (p.Arg725Trp) (PMID 18505979), or c.2646+2T>A (PMID 11738358). However, in both cases, the in trans data from these patients will be used in the classification of the other variant and was not included here in order to avoid a circular argument. Additional patients have been reported but were not included because the residual GAA activity was not reported and therefore PP4 cannot be assessed (PMIDs 25998610, 27711114, 30022036). There is a ClinVar entry for this variant (Variation ID: 370276; 1 star review status) with one submitter classifying the variant as likely pathogenic. 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, PP4.

Met criteria codes

PM2	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 (Latino) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PVS1	✔	This variant is predicted to result in a premature stop codon that is detected by nonsense mediated decay resulting in lack of gene product, meeting PVS1.
PP4	✔	Two individuals have been reported with this variant and <30% normal GAA activity in cultured fibroblasts (PMIDs 11738358, 18505979). This meets the ClinGen LSD VCEP's specifications for PP4. PubMed:18505979 PubMed:11738358

Not Met criteria codes

PM3	✖	Two patients meeting the ClinGen LSD VCEP's specifications for PP4 have been reported. These patients are compound heterozygous for the variant and either c.2173C>T (p.Arg725Trp) (PMID 18505979), or c.2646+2T>A (PMID 11738358). However, in both cases, the in trans data from these patients will be used in the classification of the other variant and was not included here in order to avoid a circular argument. Additional patients have been reported but were not included because the residual GAA activity was not reported and therefore PP4 cannot be assessed (PMIDs 25998610, 27711114, 30022036). This variant was found in 2 patients with c.-32-13T>G. c.-32-13T>G is a well-known pathogenic variant. The phase of the variants was not confirmed. The patient does not meet PP4 criteria, therefore no points were awarded. PubMed:25998610

Curation History

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