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Variant: NM_000152.5(GAA):c.1496G>A (p.Trp499Ter)

Version: 1.0

CA8815357

556959 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 967a4b39-aeb4-4f91-bc24-14484107bf7e
Approved on: 2020/10/5
Published on: 2020/11/12

HGVS expressions

NM_000152.5:c.1496G>A
NM_000152.5(GAA):c.1496G>A (p.Trp499Ter)
NC_000017.11:g.80110785G>A
CM000679.2:g.80110785G>A
NC_000017.10:g.78084584G>A
CM000679.1:g.78084584G>A
NC_000017.9:g.75699179G>A
NG_009822.1:g.14230G>A
ENST00000570803.6:c.1496G>A
ENST00000572080.2:c.1496G>A
ENST00000577106.6:c.1496G>A
ENST00000302262.8:c.1496G>A
ENST00000302262.7:c.1496G>A
ENST00000390015.7:c.1496G>A
NM_000152.3:c.1496G>A
NM_001079803.1:c.1496G>A
NM_001079804.1:c.1496G>A
NM_000152.4:c.1496G>A
NM_001079803.2:c.1496G>A
NM_001079804.2:c.1496G>A
NM_001079803.3:c.1496G>A
NM_001079804.3:c.1496G>A

Pathogenic

Met criteria codes 4

PM2 PM3_Supporting PVS1 PP4

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.1496G>A (p.Trp499Ter) is a nonsense variant which is predicted to cause nonsense mediated decay resulting in lack of gene product. This is supported by the absence of cross reactive immunological material in cultured skin fibroblasts from a patient with this variant (PMIDs 19775921, 22252923, and 25741864). Therefore, PVS1 can be applied. This patient, who has infantile onset Pompe disease, meets the ClinGen LSD VCEP's specifications for PP4, and is homozygous for the variant, meeting PM3_Supporting. Additional patients have been reported, including 2 homozygous Tunisian patients (PMID 32125626), but the residual GAA activity was not provided, and this data was not included. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 in the Latino population, which meets PM2. There is a ClinVar entry for this variant (Variation ID 556959, 1 star review status), with one submitter classifying the variant as pathogenic and one as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, based on the specifications of the ClinGen LSD VCEP: PVS1, PM2, PM3_Supporting, 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.
PM3_Supporting	✔	One patient with Pompe disease and meeting the ClinGen LSD VCEP's specification for PP4 has been reported. This patient has infantile onset Pompe disease, is homozygous for the variant, and has no GAA cross-reactive immunological material in cultured skin fibroblasts (PMIDs 19775921, 22252923, and 25741864). Additional patients have been reported, including 2 homozygous Tunisian patients (PMID 32125626), but the residual GAA activity was not provided. Based on this data, 0.5 points were given for PM3, meeting PM3_Supporting.
PVS1	✔	This is a nonsense variant which is predicted to cause nonsense mediated decay resulting in no gene product. This is supported by the absence of GAA cross reactive immunological material in fibroblasts in a patient with this variant (PMIDs 19775921, 22252923, and 25741864). Therefore, PVS1 can be applied.
PP4	✔	One patient has been reported with Pompe disease and <1% GAA activity in cultured skin fibroblasts and/or muscle (PMID 19775921, 25741864). This meets the ClinGen LSD VCEP's specifications for PP4. Additional patients have been reported but the residual GAA activity was not provided (PMID 18425781, 32125626).

Curation History

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