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Variant: NM_000152.5(GAA):c.1411_1414del (p.Glu471fs)

Version: 1.0

CA274067

188874 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 945730af-c6de-4db4-8be4-afb5df17ff92
Approved on: 2020-10-08
Published on: 2020-11-12

HGVS expressions

NM_000152.5:c.1411_1414del
NM_000152.5(GAA):c.1411_1414del (p.Glu471fs)
NC_000017.11:g.80110029_80110032del
CM000679.2:g.80110029_80110032del
NC_000017.10:g.78083828_78083831del
CM000679.1:g.78083828_78083831del
NC_000017.9:g.75698423_75698426del
NG_009822.1:g.13474_13477del
ENST00000570803.6:c.1411_1414del
ENST00000572080.2:c.1411_1414del
ENST00000577106.6:c.1411_1414del
ENST00000302262.8:c.1411_1414del
ENST00000302262.7:c.1411_1414del
ENST00000390015.7:c.1411_1414del
NM_000152.3:c.1411_1414del
NM_001079803.1:c.1411_1414del
NM_001079804.1:c.1411_1414del
NM_000152.4:c.1411_1414del
NM_001079803.2:c.1411_1414del
NM_001079804.2:c.1411_1414del
NM_001079803.3:c.1411_1414del
NM_001079804.3:c.1411_1414del

Pathogenic

Met criteria codes 3
PVS1 PP4 PM2

Not Met criteria codes 1
PM3

Evidence Links 14

Expert Panel
Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.1411_1414del (p.Glu471ProfsTer5), is a frameshift variant that is predicted to result in a premature termination codon, nonsense mediated decay, and lack of gene product. Therefore, PVS1 can be applied. The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002513 in the East Asian population, meeting PM2. This variant has been reported multiple times in Asian patients with Pompe disease presenting clinically and identified by newborn screening. At least eight patients with Pompe disease and meeting the ClinGen LSD VCEP's specifications for PP4 have been reported as compound heterozygous with either c.214C>A (p.Leu141Met), c.872T>C, (p.Leu291Pro), c.1933G>C (p.Asp645His), or c.1935C>A (p.Asp645Glu) (PMIDs 8604985, 18458862, 24243590, 31510962). The in trans data for these patients will be used in the assessment of the missense variants and, therefore, was not included here in order to avoid circular logic. Additional patients with this variant have been reported but were not included because no residual GAA activity provided and, therefore, PP4 could not be assessed (PMIDs 10338092, 25466677, 27183828, 27692865, 28394184, 29122469), or pseudodeficiency alleles are present (PMID 19948615, 21232767, 23632029, 27183828). Of note, the variant has been reported to be in cis with two missense changes, c.[752C>T; 761C>T] (p.[Ser251Leu; Ser254Leu]) (PMIDs 20080426, 25466677, 27183828, 29122469). There is a ClinVar entry for this variant (Variation ID: 188874, 2 star review status) with three submitters 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. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PVS1, PM2, PP4.

Met criteria codes

PVS1	✔	This is a frameshift variant which is predicted to result in a premature termination codon, nonsense mediated decay, and lack of gene product. Therefore, PVS1 can be applied.
PP4	✔	At least eight patients with Pompe disease and meeting the ClinGen LSD VCEP's specifications for PP4 have been reported (PMIDs 8604985, 18458862, 24243590, 31510962). PubMed:29122469 PubMed:25466677 PubMed:10338092
PM2	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002513 in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.

Not Met criteria codes

PM3	✖	This variant has been reported multiple times in Asian patients with Pompe disease, either presenting clinically or identified by newborn screening. At least eight patients with Pompe disease and meeting the ClinGen LSD VCEP's specifications for PP4 have been reported as compound heterozygous with either c.214C>A (p.Leu141Met), c.872T>C, (p.Leu291Pro), c.1933G>C (p.Asp645His), or c.1935C>A (p.Asp645Glu) (PMIDs 8604985, 18458862, 24243590, 31510962). The in trans data for these patients will be used in the assessment of the missense variants and, therefore, was not included here in order to avoid circular logic. Additional patients with this variant have been reported but were not included because no residual GAA activity provided and, therefore, PP4 could not be assessed (PMIDs 10338092, 25466677, 27183828, 27692865, 28394184, 29122469), or pseudodeficiency alleles are present (PMID 19948615, 21232767, 23632029, 27183828). Of note, the variant has been reported to be in cis with two missense changes, c.[752C>T; 761C>T] (p.[Ser251Leu; Ser254Leu]) (PMIDs 20080426, 25466677, 27183828, 29122469). Based on this data, PM3 is not currently met. PubMed:18458862 PubMed:20080426

PubMed:23632029
PubMed:8604985
PubMed:28394184
PubMed:27692865
PubMed:24243590
PubMed:27183828
PubMed:31510962
PubMed:21232767
PubMed:19948615

Curation History

Showing 1 to 1 of 1 rows