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Variant: NM_000152.5(GAA):c.1822C>T (p.Arg608Ter)

Version: 1.0

CA8815488

972803 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 01fbc615-8e60-4987-ab1a-988de4e3e661
Approved on: 2021/10/26
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HGVS expressions

NM_000152.5:c.1822C>T
NM_000152.5(GAA):c.1822C>T (p.Arg608Ter)
NC_000017.11:g.80112645C>T
CM000679.2:g.80112645C>T
NC_000017.10:g.78086444C>T
CM000679.1:g.78086444C>T
NC_000017.9:g.75701039C>T
NG_009822.1:g.16090C>T
ENST00000570803.6:c.1822C>T
ENST00000572080.2:c.1822C>T
ENST00000577106.6:c.1822C>T
ENST00000302262.8:c.1822C>T
ENST00000302262.7:c.1822C>T
ENST00000390015.7:c.1822C>T
ENST00000570716.1:n.262C>T
ENST00000572080.1:c.210C>T
ENST00000572803.1:n.436C>T
NM_000152.3:c.1822C>T
NM_001079803.1:c.1822C>T
NM_001079804.1:c.1822C>T
NM_000152.4:c.1822C>T
NM_001079803.2:c.1822C>T
NM_001079804.2:c.1822C>T
NM_001079803.3:c.1822C>T
NM_001079804.3:c.1822C>T

Pathogenic

Met criteria codes 4

PM2_Supporting PVS1 PP4_Moderate PM3_Strong

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1822C>T (p.Arg608Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 13/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. This variant has been identified in a patient with no GAA cross reactive immunological material in skin fibroblasts supporting that it is a loss of function variant (PMIDs 22252923, 32849613)(PVS1). This variant has been detected in at least 13 individuals reported to have Pompe disease. At least 10 patients, mostly East Asian, have been reported with features with high specificity for Pompe disease including documentation of laboratory values showing deficient GAA activity and/or clinical features consistent with infantile onset Pompe disease and/or treated with enzyme replacement therapy, all meeting the specifications for PP4_Moderate (PMID 21484825, 21940687, 23884227, 24269976, 26693141, 29124014, 29422078, 30360039, 31439017, 31875618, 32849613). Of the individuals with this variant who are reported to have Pompe disease, two individuals were compound heterozygous for the variant and a pathogenic variant; in one case, the variant was confirmed in trans with c.2662G>T (p.Glu888Ter)(PMID 31743840, ClinVar SCV SCV001371767.1), and in another case the variant was found in compound heterozygosity, phase unknown, with c.-32-13T>G (PMID 31545528)(phase unknown). Another individual was homozygous for the variant (PMID 29124014)(PM3_Strong). In addition, the variant was found in compound heterozygosity with the following variants, phase unknown - c.1935C>A (p.Asp645Glu) (PMID 24269976, 31439017), c.875A>G (p.Tyr292Cys)(PMID 21940687, 23884227, 30360039), c.1309C>T (p.Arg437Cys)(PMID 21940687, 23884227, 30360039), c.784G>A (p.Glu262Lys)(PMID 29422078), c.2238G>C (p.Trp746Cys)(PMID 28433475), c.953T>A (p.Met318Lys)(PMID 21484825), and c.1754+2T>A (PMID 26693141, 32849613), and it was confirmed in trans with c.2297A>C (p.Tyr766Ser)(PMID 31875618). The allelic data from these additional patients will be used in the assessment of the second variant and is not included here to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variant ID: 972803, 1 star review status) with two submitters classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen LSD VCEP (Specifications Version 2): PVS1, PM3_Strong, PP4_Moderate, PM2_Supporting. Classification approved by the ClinGen LSD VCEP: Oct. 19th, 2021.

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PVS1	✔	The NM_000152.5:c.1822C>T (p.Arg608Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 13/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism This variant has been identified in a patient with no GAA cross reactive immunological material in skin fibroblasts supporting that it is a loss of function variant (PMIDs 22252923, 32849613)(PVS1).
PP4_Moderate	✔	At least 10 patients have been reported with features with high specificity for Pompe disease including documentation of laboratory values showing deficient GAA activity and/or clinical features consistent with infantile onset Pompe disease and/or treated with enzyme replacement therapy, all meeting the specifications for PP4_Moderate (PMID 21484825, 21940687, 23884227, 24269976, 26693141, 29124014, 29422078, 30360039, 31439017, 31875618, 32849613). Additional patients have been reported but did not meet the specifications for PP4 (PMID 20202878, 21982629, 28433475, 31743840, 31545528).
PM3_Strong	✔	This variant has been detected in at least 13 individuals reported to have Pompe disease (10 meeting PP4_Moderate). This includes two individuals who were compound heterozygous for the variant and a pathogenic variant, in one case c.2662G>T (p.Glu888Ter)(PMID 31743840)(ClinVar SCV SCV001371767.1; confirmed in trans, 1 point), and in another case c.-32-13T>G (PMID 31545528)(phase unknown, 0.5 points). Another individual was

homozygous for the variant (PMID 29124014)(0.5 points); Total 2 points for PM3 (PM3_Strong). In addition, the variant was found in compound heterozygosity with the following variants, phase unknown - c.1935C>A (p.Asp645Glu) (PMID 24269976, 31439017), c.875A>G (p.Tyr292Cys)(PMID 21940687, 23884227, 30360039), c.1309C>T (p.Arg437Cys)(PMID 21940687, 23884227, 30360039), c.784G>A (p.Glu262Lys)(PMID 29422078), c.2238G>C (p.Trp746Cys)(PMID 28433475), c.953T>A (p.Met318Lys)(PMID 21484825), and c.1754+2T>A (PMID 26693141, 32849613), and confirmed in trans with c.2297A>C (p.Tyr766Ser)(PMID 31875618). The in trans data from these additional patients will be used in the assessment of the second variant and is not included here to avoid circular logic.

Curation History

Showing 1 to 1 of 1 rows

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