Variant: NM_000152.4(GAA):c.2238G>C (p.Trp746Cys)

Version: 1.0

CA8815665

265160 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: ad2e847c-b962-45a9-9153-2be48be47e3e
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HGVS expressions

NM_000152.4:c.2238G>C
NM_000152.4(GAA):c.2238G>C (p.Trp746Cys)
NC_000017.11:g.80117016G>C
CM000679.2:g.80117016G>C
NC_000017.10:g.78090815G>C
CM000679.1:g.78090815G>C
NC_000017.9:g.75705410G>C
NG_009822.1:g.20461G>C
ENST00000570803.6:c.2238G>C
ENST00000572080.2:c.*376G>C
ENST00000577106.6:c.2238G>C
ENST00000302262.8:c.2238G>C
ENST00000302262.7:c.2238G>C
ENST00000390015.7:c.2238G>C
ENST00000572080.1:c.657G>C
ENST00000573556.1:n.191G>C
NM_000152.3:c.2238G>C
NM_001079803.1:c.2238G>C
NM_001079804.1:c.2238G>C
NM_001079803.2:c.2238G>C
NM_001079804.2:c.2238G>C
NM_000152.5:c.2238G>C
NM_001079803.3:c.2238G>C
NM_001079804.3:c.2238G>C

Pathogenic

Met criteria codes 5

PM3_Very Strong | PP4_Moderate | PS3_Supporting | PM2_Supporting | PP3

Not Met criteria codes 1

PM5

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.2238G>C variant in GAA is a missense variant predicted to cause substitution of tryptophan by cysteine at amino acid 746 (p.Trp746Cys). This variant is one of the most commonly reported variants in patients with late onset Pompe disease from East Asia (PMIDs 21757382, 31076647) and has been reported in more than 30 patients with Pompe disease (PMIDs 7981676, 18458862, 21232767, 21757382, 25093132, 25526786, 27099502, 27692865, 28433475, 29095275, 29120458, 30360039, 30897595). Because the variant often occurs in cis with pseudodeficiency variants, a conservative approach was taken when assessing data for PP4 and PM3. When pseudodeficiency variants were present or not confirmed to be absent, GAA deficiency was not used to apply PP4, and allelic data was not used for PM3 unless there was convincing evidence that the patient has Pompe disease in addition to GAA deficiency and molecular results. At least 7 Chinese patients have been reported to have the variant and were confirmed to not carry either of the pseudodeficiency variants that are common in East Asian populations (c.1726G>A (p.Gly576Ser) and c.2065G>A (p.Glu689Lys))(PMID 25526786). The patients all had documented laboratory values showing deficiency of GAA activity (PP4_Moderate). In addition, at least 4 patients with the variant and one or both pseudodeficiency variants were reported to have clinical features consistent with Pompe disease and improvements on enzyme replacement therapy (PMIDs 21232767, 25093132, 30360039). Of these patients, 8 were compound heterozygous for the variant and a GAA variant classified as pathogenic by the ClinGen LSD VCEP, phase unknown, including c.444C>G (p.Tyr148Ter), phase unknown, (PMID 25093132), c.1356delC (note that nomenclature in the paper is c.1355delC), phase unknown, (ClinVar SCV SCV001443295.1), c.1935C>A (p.Asp645Glu)(three patients, one confirmed in trans)(PMIDs 21232767, 25526786), c.2662G>T (p.Glu888Ter)(2 patients, one confirmed in trans)(ClinVar SCV001371767.1 (PMIDs 21232767, 25526786), and c.241C>T (p.Gln81Ter), phase unknown (ClinVar SCV001443296.1)(PMID 25526786)(PM3_Very Strong). The highest population minor allele frequency in gnomAD is 0.00057 (European non-Finnish) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion (PM2_Supporting). When expressed in cultured cells, this variant has been reported to reduce GAA activity, ranging from 5-29% of the wild type activity (PMIDs 7981676, 21757382, 23430493)(PS3_Supporting). The computational predictor REVEL gives a score of 0.896, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Other missense substitutions at this amino acid position reported in patients with Pompe disease include c.2236T>C (p.Trp746Arg), c.2237G>C (p.Trp746Ser), and c.2237G>T (p.Trp746Leu). The classification for p.Trp746Cys will be used in the assessment of these other variants and therefore PM5 is not met here in order to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 265160; 2 star review status) with 14 submitters classifying the variant as pathogenic and two as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen LSD VCEP (Specifications Version 2.0): PM3_Very Strong, PP3, PP4_Moderate, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen LSD VCEP - Oct. 19, 2021).

Met criteria codes

PM3_Very Strong	✔	Of patients with GAA deficiency for whom pseudodeficiency alleles were confirmed to be absent and/or PP4 was otherwise met, 8 were compound heterozygous for the variant and a GAA variant classified as pathogenic by the ClinGen LSD VCEP, phase unknown, including c.444C>G (p.Tyr148Ter)(PMID 25093132, phase unknown, 0,5 points), c.1356delC (note that nomenclature in the paper is c.1355delC) (ClinVar SCV SCV001443295.1, 0.5 points), c.1935C>A (p.Asp645Glu)(three patients, one confirmed in trans)(PMID 21232767, 25526786; 2 points), c.2662G>T (p.Glu888Ter)(ClinVar SCV001371767.1, 2 patients, one confirmed in trans; 1 + 0.5 points)(PMIDs 21232767, 25526786), and c.241C>T (p.Gln81Ter)(ClinVar SCV001443296.1, 0.5 points)(PMID 25526786). Total points >4 (PM3_Very Strong).
PP4_Moderate	✔	Because the variant often occurs in cis with pseudodeficiency variants, a conservative approach was taken when assessing data for PP4. When pseudodeficiency variants were present or not confirmed to be absent, GAA deficiency was not used to apply PP4. At least 7 Chinese patients have been reported to have the variant and were confirmed to not carry either of the pseudodeficiency variants that are common in East Asian populations (c.1726G>A (p.Gly576Ser) and c.2065G>A (p.Glu689Lys))(PMID 25526786). The patients all had documented laboratory values showing deficiency of GAA activity (PP4_Moderate). In addition, at least 4 patients with the variant and one or both

pseudodeficiency variants were reported to have clinical features consistent with Pompe disease and improvements on enzyme replacement therapy (PMIDs 21232767, 25093132, 30360039).

PS3_Supporting	✔	When expressed in cultured cells, this variant has been reported to reduce GAA activity although the results are variable, ranging from 5-29% of the wild type activity (PMIDs 7981676, 21757382, 23430493). This variant has been reported to be in cis with the pseudodeficiency variant c.2065G>A (p.Glu689Lys). One study found that the presence of both missense substitutions in the same construct did not diminish transient expression of enzyme activity any further (12% of wild type for p.Trp746Cys alone vs 17% for both variants in cis) (PMID 7981676), while another found that the two variants in cis resulted in “barely detectable activity” (vs. 5-8% for the p.Trp746Cys alone) (PMID 21757382). On Western blot, the pattern of GAA processing was similar to wild type, although bands were less intense (PMID 23430493). Based on the specifications of the ClinGen LSD VCEP, this data meets PS3_Supporting.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD is 0.00057 (European non-Finnish) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.896, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PM5	✖	Other missense substitutions at this amino acid position reported in patients with Pompe disease include c.2236T>C (p.Trp746Arg), c.2237G>C (p.Trp746Ser), and c.2237G>T (p.Trp746Leu). The classification for p.Trp746Cys will be used in the assessment of these other variants and therefore PM5 is not met here in order to avoid circular logic.

Curation History

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