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Variant: NM_000152.5(GAA):c.1798C>T (p.Arg600Cys)

Version: 1.0

CA8815481

640911 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: c36e7ac5-eb57-42af-9970-5ed94590f028
Approved on: 2021/9/30
Published on: 2021/12/2

HGVS expressions

NM_000152.5(GAA):c.1798C>T (p.Arg600Cys)
NM_000152.5:c.1798C>T
NC_000017.11:g.80112621C>T
CM000679.2:g.80112621C>T
NC_000017.10:g.78086420C>T
CM000679.1:g.78086420C>T
NC_000017.9:g.75701015C>T
NG_009822.1:g.16066C>T
ENST00000570803.6:c.1798C>T
ENST00000572080.2:c.1798C>T
ENST00000577106.6:c.1798C>T
ENST00000302262.8:c.1798C>T
ENST00000302262.7:c.1798C>T
ENST00000390015.7:c.1798C>T
ENST00000570716.1:n.238C>T
ENST00000572080.1:c.186C>T
ENST00000572803.1:n.412C>T
NM_000152.3:c.1798C>T
NM_001079803.1:c.1798C>T
NM_001079804.1:c.1798C>T
NM_000152.4:c.1798C>T
NM_001079803.2:c.1798C>T
NM_001079804.2:c.1798C>T
NM_001079803.3:c.1798C>T
NM_001079804.3:c.1798C>T

Pathogenic

Met criteria codes 7

PM2_Supporting PP3 PM1 PM5 PS3_Moderate PP4_Moderate PM3_Strong

Not Met criteria codes 1

BA1

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.1798C>T variant in GAA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 600 (p.Arg600Cys). At least 15 patients with Pompe disease have been reported with this variant. Of these patients, at least 8 have documented laboratory values showing GAA deficiency, some of whom also have documentation of symptoms consistent with infantile onset Pompe disease, and/or on enzyme replacement therapy, meeting the ClinGen LSD VCEP's specifications for PP4_Moderate (PMID 14695532, 18458862, 19609281, 21984055, 24384324, 26497565, 29124014) (PP4_Moderate). Additional patients were reported to be on enzyme replacement therapy, without GAA activity values provided, meeting PP4 (PMID 20202878), and others were reported to have Pompe disease but did not have sufficient data for PP4 to be applied (PMID 11053688, 14643388, 26253708, 27417441, 29124014). The patients with Pompe disease and this variant include three patients who are compound heterozygous for the variant and a pathogenic variant in GAA, either c.525delT (PMID 14695532; phase unknown), or c.546G>T (PMID 20202878, 21984055; phase unknown in both cases), and one homozygote (PMID 11053688)(PM3_Strong). The variant was also reported to be in cis with c.199G>A (p.Asp67Asn) and in trans with c.546G>T in one patient; this data was not counted for PM3 due to the presence of the in cis variant, which is rare and has not yet been assessed by the LSD VCEP (PMID 19609281). In addition, the variant was found in compound heterozygosity with the following variants; the allelic data for the following patients will be used in the assessment of the second variant and is not included here to avoid circular logic - c.871C>T (p.Leu291Phe)(PMID 26253708, 27417441), c.872T>C (p.Leu291Pro)(PMID 18458862), c.1211A>G (p.Asp404Gly) (PMID 24384324), c.1309C>T (p.Arg437Cys)(PMID 29124014), c.1316T>A (p.Met439Lys)(PMID 20202878), c.1857C>G (p.Ser619Arg)(PMID 29124014), c.1979G>A (p.Arg660His)(PMID 14643388), c.2105G>T (p.Arg702Leu)(PMID 26497565), c.2481+1G>A (PMID 29124014). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 in the South Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). This variant alters an amino acid, Arg600, that has been deduced to be important in the active site architecture of GAA, based on the crystal structure of native and recombinant GAA (PMID: 29061980; DOI 10.1101/212837)(PM1). Indeed, when expressed in either COS cells or GAA-deficient SV40 immortalized fibroblasts, the variant had <1% wild type GAA activity, and Western blot showed abnormal synthesis and processing of the enzyme (PMID 11053688, 14695532) (PS3_Moderate). The computational predictor REVEL gives a score of 0.915 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Three additional missense changes in the same codon have been reported in patients with Pompe disease; c.1799G>A (p.Arg600His) is pathogenic based on assessment by the ClinGen LSD VCEP (PM5); c.1799G>C (p.Arg600Pro) and c.1799G>T (p.Arg600Leu) have also been reported. There is a ClinVar entry for this variant (Variant ID 640911; 2 star review status) with three submitters classifying the variant as 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): PM1, PM5, PP3, PS3_Moderate, PM3_Strong, PM2_Supporting, PP4_Moderate.

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 in the South Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.915 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM1	✔	This variant alters an amino acid, Arg600, that has been deduced to be important in the active site architecture of GAA, based on the crystal structure of native and recombinant GAA (PMID: 29061980; DOI 10.1101/212837) (PM1)
PM5	✔	Three additional missense changes in the same codon have been reported in patients with Pompe disease. c.1799G>A (p.Arg600His) is pathogenic based on assessment by the ClinGen LSD VCEP (PM5) as well as c.1799G>C (p.Arg600Pro) and c.1799G>T (p.Arg600Leu). The latter two variants have not yet been classified by the VCEP.

PS3_Moderate		✔	When expressed in either COS cells or GAA-deficient SV40 immortalized fibroblasts (PMID 14695532, the variant had <1% wild type GAA activity and furthermore, Western blot showed abnormal synthesis and processing of the enzyme (PMID 11053688, 14695532) (PS3_Moderate).
PP4_Moderate		✔	At least 15 patients with Pompe disease have been reported with this variant. Of these patients, at least 8 have documented laboratory values showing GAA deficiency, some of whom also have documentation of symptoms consistent with infantile onset Pompe disease, and/or on enzyme replacement therapy meeting the ClinGen LSD VCEP's specifications for PP4_Moderate (PMID 14695532, 18458862, 19609281, 21984055, 24384324, 26497565, 29124014). Additional patients were reported to be on enzyme replacement therapy (without GAA activity values provided)(PMID 20202878), and others were reported to have Pompe disease but did not have sufficient data for PP4 to be applied (PMID 11053688, 14643388, 26253708, 27417441, 29124014). Overall, PP4_Moderate.
PM3_Strong		✔	At least 15 patients with Pompe disease have been reported with this variant, including three patients who are compound heterozygous for the variant and a pathogenic variant in GAA, either c.525delT (PMID 14695532; phase unknown, 0.5 points), or c.546G>T (PMID 20202878, 21984055; phase unknown in both cases; 2 x 0.5 points), and one homozygote (PMID 11053688; 0.5 points). The variant was also reported to be in cis with c.199G>A (p.Asp67Asn) and in trans with c.546G>T in one patient; this data was not counted for PM3 due to the presence of the in cis variant, which is rare and has not yet been assessed by the VCEP (PMID 19609281). In addition, the variant was found in compound heterozygosity with the following variants; the allelic data for the following patients will be used in the assessment of the second variant and is not included here to avoid circular logic - c.871C>T (p.Leu291Phe)(PMID 26253708, 27417441), c.872T>C (p.Leu291Pro)(PMID 18458862), c.1211A>G (p.Asp404Gly) (PMID 24384324), c.1309C>T (p.Arg437Cys)(PMID 29124014), c.1316T>A (p.Met439Lys)(PMID 20202878), c.1857C>G (p.Ser619Arg)(PMID 29124014), c.1979G>A (p.Arg660His)(PMID 14643388), c.2105G>T (p.Arg702Leu) (PMID 26497565), c.2481+1G>A (PMID 29124014). Total 2 points for PM3 (PM3_Strong).

Not Met criteria codes

BA1		✖	gnomAD - 0.000004025 ExAC - 0.00001

Curation History

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