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Variant: NM_000152.4(GAA):c.1799G>A (p.Arg600His)

Version: 1.0

CA8815482

370130 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 692b25ea-7706-485c-b444-ebe61391e4b5
Approved on: 2022/10/18
Published on: 2022/10/21

HGVS expressions

NM_000152.4:c.1799G>A
NM_000152.4(GAA):c.1799G>A (p.Arg600His)
NC_000017.11:g.80112622G>A
CM000679.2:g.80112622G>A
NC_000017.10:g.78086421G>A
CM000679.1:g.78086421G>A
NC_000017.9:g.75701016G>A
NG_009822.1:g.16067G>A
ENST00000570803.6:c.1799G>A
ENST00000572080.2:c.1799G>A
ENST00000577106.6:c.1799G>A
ENST00000302262.8:c.1799G>A
ENST00000302262.7:c.1799G>A
ENST00000390015.7:c.1799G>A
ENST00000570716.1:n.239G>A
ENST00000572080.1:c.187G>A
ENST00000572803.1:n.413G>A
NM_000152.3:c.1799G>A
NM_001079803.1:c.1799G>A
NM_001079804.1:c.1799G>A
NM_001079803.2:c.1799G>A
NM_001079804.2:c.1799G>A
NM_000152.5:c.1799G>A
NM_001079803.3:c.1799G>A
NM_001079804.3:c.1799G>A

Pathogenic

Met criteria codes 6

PP3 PM1 PP4_Moderate PM3_Strong PM2_Supporting PS3_Moderate

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
PDF

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1799G>A variant in GAA is a missense variant predicted to result in substitution of arginine by histidine at amino acid 600 (p.Arg600His). This variant has been reported in at least 7 patients including those with symptoms consistent with infantile onset Pompe disease, <10% GAA activity in muscle, and showing improvement on enzyme replacement therapy (PMID: 15121988, 24715333); one patient identified on newborn screen with confirmatory GAA activity testing and showing cardiac hypertrophy and arrythmia on cardiac evaluation (PMID: 33073007), three patients with features consistent with Pompe disease and GAA activity in the laboratory's affected range in dried blood spots or leukocytes (PMID: 2267665, 33741225) (PP4_Moderate). Four patients are compound heterozygous for the variant and another variant in GAA, phase unknown, that has been classified a pathogenic by the ClinGen LSD VCEP including c.-32-13T>G (2 independent probands, PMIDs: 21967859, 2267665), c.2481+110_2646+39del) (2 independent probands, PMID: 15121988, 24715333; PMID: 2267665), and one homozygote (PMID: 33073007) (PM3_Strong). In addition, two patients are compound heterozygous for the variant and another missense change, or c.1465G>A (p.Asp489Asn) (PMID: 22711147) or c.1751A>C (p.His584Pro) (PMID: 33741225). The allelic data from these patients will be used in the assessment of the other missense change and is not included here to avoid circular logic. The amino acid change was reported in additional patients but the cDNA changes were not provided and so the data is not included (PMID: 10338092, 20033296). The highest population minor allele frequency in gnomAD is 0.00003 (1.30606 alleles) in the South Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). This variant alters the arginine at amino acid 600, a residue that crystallography studies have shown to be important important in the active site architecture and substrate binding of GAA, and therefore has been defined as a critical residue by the ClinGen LSD VCEP (https://www.biorxiv.org/content/10.1101/212837v1.full.pdf, PMID: 29061980) (PM1). This variant results in <2% GAA activity when expressed in COS-7 and HEK 293 cells (PMID: 19862843, 24715333), and was shown to be abnormally processed by Western blot analysis, with production of very little of the active 76 kDa form, when expressed in HEK293 cells (PMID: 24715333). PS3_Moderate is applied based on two separate studies, one showing GAA deficiency and the other showing abnormal GAA processing (PS3_Moderate). The computational predictor REVEL gives a score of 0.967 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. The classification of p.Arg600His will be used to to support the classification of the other variants c.1798C>T (p.Arg600Cys) (pathogenic based on classification by the ClinGen LSD VCEP), c.1799G>C (p.Arg600Pro) and c.1799G>T (p.Arg600Leu), and is not used here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 370130) with 10 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 crteria applied, as specified by the ClinGen LSD VCEP (Specification Version 2.0): PM3_Strong, PM1, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. Classification approved by the ClinGen LSD VCEP on Oct 18, 2022).

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.967 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM1	✔	This variant alters the arginine at amino acid 600, a residue that crystallography studies have shown to be important important in the active site architecture and substrate binding of GAA, and therefore has been defined as a critical residue by the ClinGen LSD VCEP (https://www.biorxiv.org/content/10.1101/212837v1.full.pdf, PMID: 29061980) (PM1)
PP4_Moderate	✔	This variant has been reported in at least 7 patients including one with symptoms consistent with IOPD (cardiac hypertrophy, axial hypotonia), <10% GAA activity in muscle, and showing improvement of cardiac hypertrophy on enzyme replacement therapy (PMID: 15121988, 24715333); one patient identified on newborn screen with

confirmatory GAA activity testing and showing cardiac hypertrophy an arrythmia on cardiac evaluation (PMID: 33073007), three patients with features consistent with Pompe disease and GAA activity in the laboratory's affected range in dried blood spots or leukocytes (PMID: 2267665, 33741225). These findings meet the ClinGen LSD VCEP's sepcifications for PP4_Moderate.

PM3_Strong	✔	Four patients are compound heterozygous for the variant and another variant in GAA, phase unknown, that has been classified a pathogenic by the ClinGen LSD VCEP including c.-32-13T>G (2 independent probands, 2 x 0.5 points, PMIDs: 21967859, 2267665), c.2481+110_2646+39del) (2 independent probands, 2 x 0.5 points, PMID: 15121988, 24715333; PMID: 2267665), and one homozygote (0.5 points, PMID: 33073007). Total points 2.5 (PM3_Strong). In addition, two patients are compound heterozygous for the variant and another missense change, or c.1465G>A (p.Asp489Asn) (PMID: 22711147) or c.1751A>C (p.His584Pro) (PMID: 33741225). The allelic data from these patients will be used in the assessment of the other missense change and is not included here to avoid circular logic. The amino acid change was reported in additional patients but the cDNA changes were not provided and so the data is not included (PMID: 10338092, 20033296).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD is 0.00003 (1.30606 alleles) in the South Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion.
PS3_Moderate	✔	This variant results in <2% GAA activity when expressed in COS-7 and HEK 293 cells (PMID: 19862843, 24715333), and was shown to be abnormally processed by Western blot analysis, with production of very little of the active 76 kDa form, when expressed in HEK293 cells (PMID: 24715333). PS3_Moderate is applied based on two separate studies, one showing GAA deficiency and the other showing abnormal GAA processing (PS3_Moderate).

Not Met criteria codes

PM5	✖	Three additional missense changes in the same codon have been reported in patients with Pompe disease. The classification of p.Arg600His will be used to to support the classification of the other variants c.1798C>T (p.Arg600Cys) (pathogenic based on classification by the ClinGen LSD VCEP), c.1799G>C (p.Arg600Pro) and c.1799G>T (p.Arg600Leu), and is not used here to avoid circular logic.

Curation History

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