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Variant: NM_000152.5(GAA):c.1979G>A (p.Arg660His)

Version: 1.1

CA274455

189172 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 02045fc7-d300-46b1-a6c6-515f7ec9f666
Approved on: 2022/3/1
Published on: 2022/7/11

HGVS expressions

NM_000152.5(GAA):c.1979G>A (p.Arg660His)
NM_000152.5:c.1979G>A
NC_000017.11:g.80112966G>A
CM000679.2:g.80112966G>A
NC_000017.10:g.78086765G>A
CM000679.1:g.78086765G>A
NC_000017.9:g.75701360G>A
NG_009822.1:g.16411G>A
ENST00000570803.6:c.1979G>A
ENST00000572080.2:c.*117G>A
ENST00000577106.6:c.1979G>A
ENST00000302262.8:c.1979G>A
ENST00000302262.7:c.1979G>A
ENST00000390015.7:c.1979G>A
ENST00000570716.1:n.419G>A
ENST00000572080.1:c.398G>A
NM_000152.3:c.1979G>A
NM_001079803.1:c.1979G>A
NM_001079804.1:c.1979G>A
NM_000152.4:c.1979G>A
NM_001079803.2:c.1979G>A
NM_001079804.2:c.1979G>A
NM_001079803.3:c.1979G>A
NM_001079804.3:c.1979G>A

Pathogenic

Met criteria codes 5

PM3_Very Strong | PP4_Moderate | PP3 | PM2_Supporting | PS3_Supporting

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.1979G>A variant in GAA is a missense variant predicted to cause substitution of arginine by histidine at amino acid 660 (p.Arg660His). More than nine individuals with features consistent with Pompe disease have been reported with this variant. Of these patients 3 probands (and two siblings) have documented laboratory values indicating GAA deficiency in the affected range in dried blood spot, or muscle, or <1% activity in cultured skin fibroblasts (PMID: 21484825, 25037089, 27649523), and three probands are reported to have low GAA activity and to be on enzyme replacement therapy (PP4_Moderate). Six patients are compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LSD VCEP. For two patients, the second variant was confirmed in trans by parental testing - c.525delT (PMID: 30559630, possibly same case in PMID: 30214072), and c.670C>T (p.Arg224Trp) (PMID: 14643388) – and in four patients the phase of the second variant is unconfirmed - c.655G>A (p.Gly219Arg) (PMID: 29122469), c.1082C>T (p.Pro361Leu) (PMID: 21484825), c.1998C>T (p.Arg600Cys) (PMID: 14643388), and c.2560C>T (p.Arg854Ter) (PMID: 30214072). Two homozygous siblings have also been reported (PMID: 27649523) (PM3_Very Strong). Two probands have been reported who are compound heterozygous for the variant and either c.-32-17_-32-10del8ins30 (PMID: 25037089; two affected siblings), or c.1114C>T (p.His372Tyr) (PMID: 30214072). The allelic data from these patients will be used in the classification 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 0.00025 (6/23566) in the African population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). In two independent studies, in which the variant was expressed in COS cells, the GAA activity was <2% wild type, indicating that the variant has a damaging effect on GAA function (PS3_Supporting). The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another variant, c.1978C>T (p.Arg660Cys), has been reported at this position. p.Arg660His will be used to support the classification of p.Arg660Cys and thus PM5 is not applied here, in order to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 189172; 2 star review status) with nine submitters classifying the variant as pathogenic, and three as likely pathogenic. In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen LSD VCEP (Specifications Version 2.0): PM3_VeryStrong, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting. (Approved by LSD VCEP on Feb 15, 2022).

Met criteria codes

PM3_Very Strong	✔	More than nine individuals with features consistent with Pompe disease have been reported with this variant. Six patients are compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LSD VCEP. For two patients, the second variant was confirmed in trans by parental testing - c.525delT (PMID: 30559630, possibly same case in PMID: 30214072) (1 point), and c.670C>T (p.Arg224Trp) (PMID: 14643388) (1 point) – and in four patients the phase of the second variant is unconfirmed - c.655G>A (p.Gly219Arg) (PMID: 29122469) (0.5 points), c.1082C>T (p.Pro361Leu) (PMID: 21484825) (0.5 points), c.1998C>T (p.Arg600Cys) (PMID: 14643388) (0.5 points), and c.2560C>T (p.Arg854Ter) (PMID: 30214072) (0.5 points). Two homozygous siblings have also been reported (PMID: 27649523) (0.5 points) Total 4.5 points (PM3_Very Strong). Two patients have been reported who are compound heterozygous for the variant and either c.-32-17_-32-10del8ins30 (PMID: 25037089), or c.1114C>T (p.His372Tyr) (PMID: 30214072). The allelic data from these two patients will be used in the classification of the second variant and is not included here to avoid circular logic.
PP4_Moderate	✔	More than nine individuals with features consistent with Pompe disease have been reported with this variant. Of these patients 3 probands (and two siblings) have documented laboratory values indicating GAA deficiency in the affected range in dried blood spot, or muscle, or <1% activity in cultured skin fibroblasts (PMID: 21484825, 25037089, 27649523) (2 points), and three probands are reported to have low GAA activity and to be on enzyme replacement therapy (1 point) (PP4_Moderate).

PP3		✔	The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM2_Supporting		✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00025 (6/23566) in the African population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PS3_Supporting		✔	In two independent studies, in which the variant was expressed in COS cells, the GAA activity was <2% wild type, indicating that the variant has a damaging effect on GAA function (PS3_Supporting).

Not Met criteria codes

PM5		✖	Another variant, c.1978C>T (p.Arg660Cys), has been reported at this position. p.Arg660His will be used to support the classification of p.Arg660Cys and thus PM5 is not applied here, in order to avoid circular logic.

Curation History

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