The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000152.4(GAA):c.670C>T (p.Arg224Trp)

Version: 1.0

CA274477

189188 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1f6327c8-2794-45a5-a3b1-4998dee695e7
Approved on: 2020/5/3
Published on: 2020/5/28

HGVS expressions

NM_000152.4(GAA):c.670C>T (p.Arg224Trp)
NM_000152.4:c.670C>T
NC_000017.11:g.80105872C>T
CM000679.2:g.80105872C>T
NC_000017.10:g.78079671C>T
CM000679.1:g.78079671C>T
NC_000017.9:g.75694266C>T
NG_009822.1:g.9317C>T
ENST00000570803.6:c.670C>T
ENST00000572080.2:c.670C>T
ENST00000577106.6:c.670C>T
ENST00000302262.8:c.670C>T
ENST00000302262.7:c.670C>T
ENST00000390015.7:c.670C>T
ENST00000570803.5:c.670C>T
NM_000152.3:c.670C>T
NM_001079803.1:c.670C>T
NM_001079804.1:c.670C>T
NM_001079803.2:c.670C>T
NM_001079804.2:c.670C>T
NM_000152.5:c.670C>T
NM_001079803.3:c.670C>T
NM_001079804.3:c.670C>T

Pathogenic

Met criteria codes 4

PM2 PS3 PP4 PM3_Strong

Not Met criteria codes 2

BP4 PP3

Evidence Links 6

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.670C>T (p.Arg224Trp) has been reported in at least 6 individuals with Pompe disease and deficient GAA activity meeting the ClinGen LSD VCEP's PP4 specifications. All of these individuals are compound heterozygous for the variant and a unique pathogenic variant, including c.-32-13T>G (PMID 25673129; phase unknown), c.525delT (PMID 12923862; phase unknown), c.763C>T (p.Gln255Ter) (PMID 25026126, confirmed in trans), c.2237G>A (p.Trp746Ter) (PMID 12923862; phase unknown), c.1064T>C (p.Leu355Pro)(PMID 23632174; confirmed in trans), and c.1979G>A (p.Arg660His) (PMID 14643388; phase unknown). These data meet PM3_Strong. Note that the in trans data from the patients with c.1064T>C (p.Leu355Pro) and c.1979G>A (p.Arg660His) will be used in the assessment of those variants and was not used here in order to avoid a circular argument. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 in the European non-Finnish population, meeting PM2. The score for the in silico meta-predictor REVEL, does not meet PP3 or BP4. However, when expressed in COS cells, this variant results in significantly reduced GAA activity, <10% of wild type (PMID 12923862, 14643388, 19862843), meeting PS3. There is a ClinVar entry for this variant (Variation ID: 189188, 1 star review status), with two submitters classifying the variant as pathogenic, one as likely pathogenic, and one as a variant of uncertain significance. In summary, the variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PS3, PM2, PM3_Strong, PP4.

Met criteria codes

PM2	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 (European non-Finnish) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PS3	✔	This variant results in significantly reduced GAA activity (<10% of wild type) when expressed in COS cells (PMID 12923862, 14643388, 19862843), meeting PS3. The variant was introduced into GAA cDNA by site directed mutagenesis and subcloned into a plasmid vector (note that only the amino acid change is provided in the paper; the cDNA change is not provided). The integrity of the insert was verified by sequencing. COS cells transfected with the variant had GAA activity of <2% normal. Controls used included mock transfected cells (negative control) and wild type cDNA (positive control). PubMed:19862843 The variant was generated by site-directed mutagenesis, confirmed by sequencing and expressed in cultured. On transient expression in COS-1 cells, the GAA activity was 34.27+/- 3.17 (n=4) which was significantly reduced compared to wild type GAA (296.50 +/-129.79) and about the same as the ALDP negative control. When stably expressed in CHO cells, GAA activity was 65.95+/-5.3 (n=6); significantly reduced compared to wild type GAA (495.97+/-331.88); CHO cells alone 32.66+/-3.94. All activities expressed as nmol/mg/h with 4-MU. (GAA activity of the variant ~6.7% of wild type as calculated by (65.95-32.66)/495.97. PubMed:12923862 The variant was expressed in COS-1 cells after site-directed mutagenesis. The presence of the variant was confirmed by sequencing. Assays were duplicated. negative controls included no vector (16.3, 18.1) and empty vector (15.1, 14.2), and positive control was wild-type GAA cDNA (245.9, 235.6). Activity of the variant was 22.8, 23.4. All activities expressed as nmol/mg protein/hr with 4-MU. PubMed:14643388
PP4	✔	At least 6 individuals with the variant have been reported with GAA activity <10% normal in muscle samples or <30% normal in cultured fibroblasts, or in the affected range in a GAA activity assay (PMIDs 12923862, 14643388, 23632174, 25026126, 25673129). This meets the specifications for PP4.
PM3_Strong	✔	At least 6 individuals with Pompe disease and deficient GAA activity meeting PP4 specifications have been reported. All of these individuals are compound heterozygous for the variant and a unique pathogenic variant, including c.-32-13T>G (PMID 25673129; phase unknown, 0.5 points), c.525delT (PMID 12923862; phase unknown, 0.5 points), c.763C>T (p.Gln255Ter) (PMID 12923862, confirmed in trans, 1 point), c.2237G>A (p.Trp746Ter) (PMID 12923862; phase unknown, 0.5 points). c.1064T>C (p.Leu355Pro)(PMID 23632174; confirmed in trans), and c.1979G>A (p.Arg660His) (PMID 14643388; phase unknown). Note that the in trans data from the patients with c.1064T>C

(p.Leu355Pro) and c.1979G>A (p.Arg660His) will be used in the assessment of those variants and was not used here in order to avoid a circular argument. Total 2.5 points, meeting PM3_Strong.

PubMed:25026126
PubMed:12923862
PubMed:14643388
PubMed:25673129
PubMed:23632174

Not Met criteria codes

BP4	✖	REVEL (in silico meta predictor for missense changes) score = 0.64 which is higher than the LSD VCEP threshold for BP4, and therefore does not meet this criterion.
PP3	✖	REVEL (in silico meta predictor for missense changes) score = 0.64 which is lower than the LSD VCEP threshold for PP3, and therefore does not meet this criterion.

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.