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Variant: NM_000152.5(GAA):c.2015G>A (p.Arg672Gln)

Version: 1.0

CA8815566

371126 (ClinVar)

Gene: GAA
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: da5aaa7a-fa4e-4ff7-9223-f3b799cd5d90
Approved on: 2022/1/4
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HGVS expressions

NM_000152.5(GAA):c.2015G>A (p.Arg672Gln)
NM_000152.5:c.2015G>A
NM_000152.5(GAA):c.2015G>A
NC_000017.11:g.80113002G>A
CM000679.2:g.80113002G>A
NC_000017.10:g.78086801G>A
CM000679.1:g.78086801G>A
NC_000017.9:g.75701396G>A
NG_009822.1:g.16447G>A
ENST00000570803.6:c.2015G>A
ENST00000572080.2:c.*153G>A
ENST00000577106.6:c.2015G>A
ENST00000302262.8:c.2015G>A
ENST00000302262.7:c.2015G>A
ENST00000390015.7:c.2015G>A
ENST00000570716.1:n.455G>A
ENST00000572080.1:c.434G>A
NM_000152.3:c.2015G>A
NM_001079803.1:c.2015G>A
NM_001079804.1:c.2015G>A
NM_000152.4:c.2015G>A
NM_001079803.2:c.2015G>A
NM_001079804.2:c.2015G>A
NM_001079803.3:c.2015G>A
NM_001079804.3:c.2015G>A

Likely Pathogenic

Met criteria codes 6

PP3 PM3_Strong PP4_Moderate PS3_Supporting PM2_Supporting PM5_Supporting

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.2015G>A variant in GAA is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 672 (p.Arg672Gln). At least 8 probands with Pompe disease have been reported with this variant, including 4 probands and one sibling with published data showing GAA activity below the normal range in muscle or cultured fibroblasts (PMID: 9535769, 17092519, 33578445), three of whom also showed clinical improvement on enzyme replacement therapy (PMID 33578445)(PP4_Moderate). Five probands are homozygous for the variant (PMIDs 9535769, 25712382, 28937052, 33578445). Two probands are compound heterozygous for the variant and a pathogenic variant in GAA; the second variant is either c.118C>T (p.Arg40Ter)(ClinVar SCV001371737.1)(phase unknown), or c.1857C>G (p.Ser619Arg)(phase unknown)(PM3_Strong). Another proband is heterozygous for the variant with the second variant unidentified (PMID 11053688). When generated by site-directed mutagenesis and expressed in SV40-immortalized GAA deficient fibroblasts or COS cells, the variant resulted in very low (<2%) residual GAA activity (PMID 9535769, 19862843) (PS3_Supporting). The computational predictor REVEL gives a score of 0.955 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). The highest population minor allele frequency in gnomAD is 0.0001107 (East Asian) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting (PM2_Supporting). Two other missense variants at the same amino acid position, c.2014C>T (p.Arg672Trp) and c.2015G>T (p.Arg672Leu)(PMID 29122469), have been reported in patients with Pompe disease, suggesting that this residue may be important in GAA function. Two other missense variants, c.2014C>T (p.Arg672Trp) and c.2015G>T (p.Arg672Leu)(PMID 29122469), have been reported at the same amino acid position; c.2014C>T (p.Arg672Trp) has been classified as pathogenic for Pompe disease by the ClinGen LSD VCEP. PM5_Supporting is applied here because c.2014C>T (p.Arg672Trp) is only likely pathogenic without PM5 data from c.2015G>A (p.Arg672Gln), thus avoiding circular logic (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 371126, 2 star review status) with 3 submitters classifying the variant as pathogenic and one as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Storage Disorders VCEP (Specifications Version 2.0): PM3_Strong, PP4_Moderate, PP3, PM2_Supporting, PM5_Supporting.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.955 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3_Strong	✔	Five probands are homozygous for the variant (PMIDs 9535769, 25712382, 28937052, 33578445)(max 1 point). Two probands are compound heterozygous for the variant and a pathogenic variant in GAA; the second variant is either c.118C>T (p.Arg40Ter)(ClinVar SCV001371737.1)(phase unknown, 0.5 points), or c.1857C>G (p.Ser619Arg)(phase unknown, 0.5 points), and one proband is heterozygous for the variant with the second variant unidentified (PMID 11053688). Total 2 points (PM3_Strong).
PP4_Moderate	✔	At least 8 probands with Pompe disease have been reported with this variant, including 4 probands and one sibling with published data showing GAA activity below the normal range in muscle or cultured fibroblasts (PMID: 9535769, 17092519, 33578445), three of whom also showed clinical improvement on enzyme replacement therapy (PMID 33578445)(PP4_Moderate).
PS3_Supporting	✔	When generated by site-directed mutagenesis and expressed in SV40-immortalized GAA deficient fibroblasts or COS cells, the variant resulted in very low (<2%) residual GAA activity (PMID 9535769, 19862843) (PS3_Supporting).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001107 (East Asian) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting.
PM5_Supporting	✔	

Two other missense variants, c.2014C>T (p.Arg672Trp) and c.2015G>T (p.Arg672Leu)(PMID 29122469), have been reported at the same amino acid position; c.2014C>T (p.Arg672Trp) has been classified as pathogenic for Pompe disease by the ClinGen LSD VCEP. PM5_Supporting is applied here because c.2014C>T (p.Arg672Trp) is only likely pathogenic without PM5 data from c.2015G>A (p.Arg672Gln), thus avoiding circular logic (PM5_Supporting).

Curation History

Showing 1 to 1 of 1 rows

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