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Variant: NM_000152.4(GAA):c.925G>A (p.Gly309Arg)

Version: 1.2

CA273972

188797 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: de8ae80b-693a-4177-8218-1d731456b97c
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HGVS expressions

NM_000152.4(GAA):c.925G>A (p.Gly309Arg)
NM_000152.4:c.925G>A
NC_000017.11:g.80107866G>A
CM000679.2:g.80107866G>A
NC_000017.10:g.78081665G>A
CM000679.1:g.78081665G>A
NC_000017.9:g.75696260G>A
NG_009822.1:g.11311G>A
ENST00000570803.6:c.925G>A
ENST00000572080.2:c.925G>A
ENST00000577106.6:c.925G>A
ENST00000302262.8:c.925G>A
ENST00000302262.7:c.925G>A
ENST00000390015.7:c.925G>A
NM_000152.3:c.925G>A
NM_001079803.1:c.925G>A
NM_001079804.1:c.925G>A
NM_001079803.2:c.925G>A
NM_001079804.2:c.925G>A
NM_000152.5:c.925G>A
NM_001079803.3:c.925G>A
NM_001079804.3:c.925G>A

Pathogenic

Met criteria codes 5

PM3_Very Strong | PP4_Moderate | PS3 | PP3 | PM2_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.925G>A variant in GAA is a missense variant predicted to cause substitution of glycine by arginine at amino acid 309 (p.Gly309Arg). In a cohort of 54 Dutch patients with Pompe disease, the allele frequency of the variant was 5.5%, and evidence suggests that it is a founder variant in that population (PMID 9660056). This variant has been reported in more than 13 individuals diagnosed with Pompe disease; for at least 6 individuals, residual GAA activity is available and is in the deficient range (PMIDs 9660056, 16838077, 23430847, 23601496, 24495340, 27189384), with some patients also reported to be on enzyme replacement therapy and/or to have documentation of symptoms consistent with infantile onset Pompe disease (PMID 23402890, 23430847, 23601496, 24495340) (PP4_Moderate). More data is available in the literature but the maximum strength of evidence for PP4, as specified by the ClinGen LSD VCEP, can already be applied.. Ten of these individuals are compound heterozygous for the variant and a pathogenic variant (PMID: 9660056, 16838077, 16917947, 23402890, 23430847), phase unknown in all cases, and one is homozygous (PMID: 23601496)(PM3_Very strong). The highest continental 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_Supporting. In functional studies, when expressed in COS cells, this variant resulted in no increase in GAA activity and showed evidence of abnormal processing (PMIDs 9660056, 19862843)(PS3_Moderate). The computational predictor REVEL gives a score of 0.963, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 188797; 2 star review status) with 8 submitters all classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP (Specifications Version 2.0): PM3_Very Strong, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Classification approved on August 17, 2021)

Met criteria codes

PM3_Very Strong	✔	This variant has been detected in more than 13 individuals with Pompe disease. Ten of those individuals were compound heterozygous for the variant and a pathogenic variant, phase unknown in all cases, including a full gene deletion (PMID 23402890, in trans, 1 point), c.525delT (PMID 9660056, 2 cases, 2 x 0.5 points), deletion of exon 18 (3 cases, score a maximum of 2 cases, 2 x 0.5), c.-32-13T>G (PMID PMID 9660056, 16838077, 16917947, score a maximum of 2 cases, 2 x 0.5 points), c.2269C>T (p.Gln757Ter) (PMID 23430847, 0.5 points), and one is homozygous for the variant (PMID 23601496, 0.5 points). Total 5 points (PM3_Very Strong). More data is available in the literature but the maximum strength of evidence for PM3, as specified by the ClinGen LSD VCEP, can already be applied.
PP4_Moderate	✔	This variant has been reported in more than 13 individuals diagnosed with Pompe disease; for at least 6 individuals, residual GAA activity is available and is in the deficient range (PMIDs 9660056, 16838077, 23430847, 23601496, 24495340, 27189384), with some patients also reported to be on enzyme replacement therapy and/or to have documentation of symptoms consistent with infantile onset Pompe disease (PMID 23402890, 23430847, 23601496, 24495340) (PP4_Moderate). More data is available in the literature but the maximum strength of evidence for PP4, as specified by the ClinGen LSD VCEP, can already be applied.
PS3	✔	In two studies, when expressed in COS cells, this variant resulted in no increase in GAA activity and showed evidence of abnormal processing (PMIDs 9660056, 19862843), meeting PS3.
PP3	✔	The computational predictor REVEL gives a score of 0.963, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM2_Supporting	✔	The highest continental 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 (applied at Supporting)

Curation History

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